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&

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SYMPOSIUM ON TRANQUILIZING AGENTS IN CLINICAL MEDICINE

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Chlorpromazine in General Practice — FRANK J. BONELLO

Use of the Tranquilizing Properties of Reserpine: A Review — J. CAMPBELL HOWARD, JR., AND FRANK J. VINCI

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FELIX MARTI-IBAÑEZ, M.D., Editor

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SYMPOSIUM ON TRANQUILIZING AGENTS IN CLINICAL MEDICINE

The New Pharmacologic Attack in Psychiatry*

Howard D. Fabing, M.D.

CHIEF, NEUROPSYCHIATRIC DEPARTMENT, CHRIST HOSPITAL
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At the outset it should be stated that the new pharmacologic attack in psychiatry is not really very new after all. The ancient Greek and Roman texts and the herbals that began to appear in medieval times and continued to be written in this country until the last century are filled with the praises of a host of roots, leaves, flowers, and seeds that were said to relieve the mind of man when it was sick. Burton's *Anatomy of Melancholy*, which Sir William Osler kept at his bedside, and which he regarded as one of the world's most scholarly books, is a vivid example of the physician's search for psychiatric drugs in the world of botany. Burton's advocacy of the hellebore, or buttercup, family in the treatment of melancholia was enthusiastic.

The bromides were introduced into therapeutics in 1857, perhaps the first generally accepted chemical agent in the treatment of disorders of the nervous system. They attained a great vogue until it was determined that they could cause more serious mental illness on occasion than they attempted to treat. The next step occurred shortly after the turn of the century. The story is told that the famous German chemist, Emil Fischer, "dreamed up" the formula for the barbiturates while he was dozing in a railway carriage on a holiday in Italy. He looked out the window and saw that he was in the station in Verona, and so he named the new compound Veronal. From this came phenobarbital, which is still one of the very best drugs we have, and which few clinicians have been able to abandon, try as they may.

The practicing physician has always been fascinated by the fact that drugs which act primarily on the central nervous system are often two-edged swords. They tranquilize and they sedate for the most part, which is satisfying, but they may excite and intoxicate too, which is not so satisfying. This mystery has never been explained adequately. In our search for specificity of action of neurotropic drugs,

* Based on a paper read at the meeting of the American Pharmaceutical Manufacturers' Association, December 1955.

we encounter the uncomfortable fact that we are dealing with an organ that is lacking in specificity in its very nature, the human brain. This does not make the pharmacologists very happy.

Pharmacologists, as I know them, are people with very neat and orderly minds. They have been trained to hook an animal up to a kymograph and get some very nice squiggles on a piece of recording paper. Then they introduce a drug of some sort and obtain a very prompt and clear-cut change in the squiggles. Unfortunately, this does not work with the brain in most cases, as it does with the heart, the gut, or the urinary bladder. In the new field of neuropharmacology, or psychopharmacology as some are wont to call it, a whole new set of tools is needed. Men like Evarts, Heath, Marrazzi, and Himwich are finding interesting new microelectrical methods for studying drug action in the brains of animals and man, though much of the action of these new compounds depends on a close scrutiny of total behavior, and much of it requires the human being as the experimental animal. Neuropharmacology is new pharmacology. It requires a fresh point of view and the willingness to keep ever on the alert for the chance observation that may open new doors to the uninhabited rooms of our house of ignorance.

This kind of fortuitous observation, or serendipity, occurred in 1943 and, in my opinion, touched off much of the new inquiry into drug effects on the brain. Hoffmann, working in the Sandoz Laboratories in Basle, Switzerland, sucked up something in his mouth from a pipette. He had been working with ergot extracts and was making esters of one of its components, lysergic acid. In less than an hour he was muddled, confused, and hallucinated. Frightened, he left the laboratory and got on his bicycle. He pedaled what seemed like 5000 miles to his home, which was in reality a short distance away, but he had lost time and space perception. He called his doctor, who managed to get him to gulp down all the milk in the house, but his psychotic state persisted until he fell into a fitful sleep late that night. Four days later he returned to his laboratory, looked over his notebooks, and decided that he had swallowed the dextrorotatory diethylamide of lysergic acid. Gingerly he measured out a very minute amount of the material and took another swallow. The psychosis returned, this time worse. He pedaled 10,000 miles home, and again drank all the milk in sight to no avail. Thus LSD-25 was born. Here was an experimental way of producing a psychosis that had very much the look and feel of schizophrenia. It takes about one seven-hundred-millionth of a healthy young man's weight of this material to produce a model psychosis lasting five to ten hours.

The minuteness of the dose and the magic of its effects have been tested and retested all over the world. One would have to be a stick or a stone not to have his imagination completely captivated by the drama of an LSD psychosis. Hoffmann's observation has fired clinicians, chemists, enzymologists, and pharmacologists into new activity everywhere. It has caused us to take a new look into old things. Experimentation with mescaline, which had languished for the most part since the days of Weir Mitchell, has now picked up again. I know of two laboratories that are making a major study of this compound and its possible derivatives. A new look at the ancient narcotic snuff of Hispaniola and South America, cohoba, has shown that it contains bufotenin, a substance first found in the skin of poisonous

toads. No self-respecting medieval Italian poisoner would have left toad skin out of his brew. Recently it has been determined that the hallucinogenic mushrooms also contain bufotenin, and that this substance was probably behind the tribal debauches, characterized by temporary madness, that were indulged in by people as diverse as the Koryaks of Siberia and the Aztecs of Mexico, and perhaps even the Vikings of the north countries. Just two months ago some murderers at the Ohio State Penitentiary volunteered for intravenous injection of bufotenin, which was kindly supplied to us by the Research Department of The Upjohn Company, and we found that it produced a temporary psychosis reminiscent of mescaline and LSD-25.

The metabolites of adrenalin have also come under scrutiny of late, especially in the schizophrenia research program in Saskatchewan, Canada. A very tricky compound, adrenochrome, has been found by this group of investigators to produce temporary schizophrenia-like psychoses of as much as four days' duration. A search through anthropologic lore reveals that other compounds, such as yohimbine, harmine, and ibogaine, have been used by man to transport himself into ecstatic states of visionary experience, through the doors of perception to the land of otherworldliness, as Aldous Huxley puts it. Nobody will contend that these states are schizophrenia, but they are very similar, and they can be studied under controlled experimental conditions. In all this, one senses the beginnings of a new scientific approach in psychiatry.

One of the fascinating things about these hallucinogenic drugs is that they are indoles. Are all indoles hallucinogenic for man? Emphatically, no! They are very common compounds in nature, ranging from the indigo dyes to auxin, the plant growth hormone, to skatole, which gives manure its stink, to serotonin, a neurohumeral agent that is under intensive study these days. The list of indoles in biology is tremendous. They are all very reactive compounds and seem capable of changing from one to the other easily.

This tantalizing thought arises: rather than being a disease we worry and fret ourselves into, is schizophrenia perhaps a biochemical disease, a disease of metabolic error, a disease caused by the production of abnormal indoles in the bodies of people —indoles that poison the brain and thereby produce the clinical picture of schizophrenia? It is only a thought, but as the evidence mounts, it becomes a more respectable thought, worthy of the most intensive research effort. If a mechanism such as this can be established, specific drug therapy cannot be far off. The stakes are high. The making of productive citizens—taxpayers instead of tax spenders—out of this large mass of cruelly afflicted patients would probably go down as one of the greatest triumphs of the twentieth century for the medical and pharmaceutical professions.

Paralleling these inquiries into the hallucinogenic drugs during the postwar period have been the strikes of drug discovery with which you are all acquainted. Reserpine, which comes from the herbal medicine of the Orient, is a very complex compound and is also an indole. Its basic structure is similar to that of yohimbine, one of the hallucinogens. Reserpine is yohimbine with a complex phenolic radical attached. Under certain experimental conditions it is a serotonin antagonist, and some workers believe that is the way it acts. It has produced some excellent thera-

peutic effects in chronically ill patients in mental hospitals. The studies of Kline at Rockland State Hospital in New York and of Pennington in Mississippi are especially encouraging. Large doses of the drug are necessary to bring about these effects.

In office practice, the side reactions of reserpine often lead one to defeat. Despite careful forewarning of patients about nasal stuffiness, drowsiness, and dizziness, when these things begin to occur the telephone almost jangles off the hook. On the next visit the patient often reports that he gave it up because of its unpleasantness. Blood pressures can fall quite low with this drug, and must be watched carefully. Perhaps the most difficult complication encountered with it is the mental depression it can produce. My colleagues and I have been concerned about this, as have other clinicians, and we have had to resort to electroshock therapy on occasion to circumvent it. Despite these difficulties, reserpine has found a real place in therapy in psychiatry.

Chlorpromazine has had a very wide use in the past two or three years. One of the most earnest students of this drug is a colleague of mine in Cincinnati, Dr. Douglas Goldman. He is the medical director of a very large, overcrowded, understaffed state institution, Longview Hospital. He has taken a new lease on life lately. The reduction in assaults, the lessened use of restraint, the increased granting of privileges to locked-ward patients, the lessened need for repeated electroshock treatment to control explosive behavior, and the beginnings of an improved discharge rate of patients from the hospital all stem from the use of this drug in his hands, and parallel the kind of improved state of affairs that Kline reports with reserpine at Rockland.

Goldman likes to tell the story about Willie. Willie was a disheveled, mute, untidy schizophrenic who had to be spoon fed and who managed to tear off just about all the clothes anyone tried to put on him. Willie received an eight week trial with chlorpromazine, but at the end of that time Goldman was not greatly impressed with this improvement. He announced that he was going to withdraw Willie's drug, whereupon an orderly raised a clamor, pleading for its continuance and insisting that Willie was much better. He said, "Wait a minute. I'll prove it to you. I'll get Johnny." In a moment he returned with Willie's identical twin. "See, they were both alike two months ago," he said. They stood side by side. Johnny's hair fell in his face, he was soiled, his pants were torn, and he was barefoot. Willie was fully clothed, barbered, shaved, clean, and wore shoes. The difference was obvious. Instead of taking a patient off chlorpromazine, Goldman put another on it.

In office practice this drug is harder to manage than in a hospital setting. The complications of skin rash, drowsiness, dizziness, apathy, jaundice, and parkinsonism, among others, tend to discourage some patients and their families from its use. Again, mental depression has a way of arising on occasion. This requires electroconvulsive treatment if mere withdrawal of the drug does not alleviate it. Despite this, it is a heartening new therapeutic tool that is welcomed gladly. The mode of action of this compound has defied explanation. If this were known, it seems plausible that other analogues of chlorpromazine, having fewer side reactions and greater efficacy, could be synthesized and applied.

For the past 18 months we have been worrying along with another of the tranquilizing drugs, or ataraxics, as I have called them. This word comes from the Greek, *ataraxia*, which means "freedom from confusion" or "peace of mind," or "detached serenity," as Ivan Bennett has translated it. For one like myself who has lived for a score of years through all kinds of therapeutic attempts in psychiatry, these drugs have constituted a new order of experience, so different have they been from anything in the past. I felt that we needed a new word to encompass their action, and thus comes the term "ataraxics."

Among the tranquilizing drugs, Frenquel* has been dramatic in its efficacy in some 40 per cent of acute schizophrenic syndromes. It has been less valuable in the chronic cases. We have found that it will block the development of an LSD or a mescaline psychosis when given as premedication in a small number of experiments, and will abort these reactions when given intravenously. Some investigators have confirmed this; others do not agree. A larger number of experiments will probably prove that Frenquel has this blocking effect in some cases but not in all of them.

Frenquel has been almost uniformly good in relieving approximately 75 cases of postoperative psychoses. Other confusional states respond well also. After having dramatic success with 2 cases of delirium tremens, we looked for others but could not find them. Proctor, at the Bowman Gray School of Medicine in Winston-Salem, has relieved 16 of 19 cases of delirium tremens quickly with Frenquel. Senile patients often go through troublesome confusional periods. Frenquel has helped us also with these on many occasions. One advantage of this drug is that it produces no side reactions.

This brings us to a consideration of another group of new compounds acting on the central nervous system, the cerebral stimulants or euphoriants. Alcohol is the most widely used of these, but it is completely unreliable in its effects. Rather than stimulate, it depresses some brains and makes others wild. Cannabis, mescaline, and bufotenin-containing mushrooms have all been used for the same purpose and are equally unpredictable.

The advent of the amphetamines marked a new step in the search for mood-elevating drugs, and they have won a place for themselves in therapy. For the past three years we have been studying one of the precursors of Frenquel, another piperidyl compound, Meratran.† It has an action similar to the amphetamines but does not cause loss of appetite and does not affect blood pressure and pulse rate. Ritalin,‡ another compound of this family, has similar properties. It was our hope in the beginning that these drugs would provide us with a new method of attack in melancholia, but they have fallen short of the mark.

In all the attention given to schizophrenia, the other great functional psychosis, melancholia, has been neglected. Although schizophrenia is a far more chronic

* The trade name of the Wm. S. Merrell Company for α-(4-piperidyl) benzhydrol hydrochloride is Frenquel.

† The trade name of the Wm. S. Merrell Company for α-(2-piperidyl) benzhydrol hydrochloride is Meratran.

‡ The trade name of Ciba Pharmaceutical Products, Inc., for methyl-phenidylacetate is Ritalin.

disease, and although it fills more long term hospital beds, melancholia is a more common disorder. My associates and I who can best be described as general practitioners of disorders of the nervous system, encompassing the fields of neurology and psychiatry, find that we encounter at least 4 or 5 new cases of melancholia for every 1 of schizophrenia. I am just as amazed at a case I saw last week as at those I saw as a student. Why or how can a normal hard-working man or woman suddenly be thrown into a state of disturbed sleep and disordered mood that is completely disabling? It can happen between a Tuesday and a Thursday. These people suddenly lose their power to concentrate their minds on the simplest activity such as reading the evening newspaper, they find all social intercourse painful and give up their friends, they believe that they are burdens on their loved ones, they develop the most illogical feelings of guilt and sin, and they stop eating. Unless something is done about them, suicide occurs all too frequently. In the days before shock therapy was introduced, patients and their families crawled through months and even years waiting for the *vis medicatrix naturae*, the curative power of nature, to put these depressed minds back on the normal track again. Electroshock therapy has compressed these attacks into a matter of a few weeks, and depressed patients seldom gravitate to the back wards of state hospitals any more. But they are still with us, and although electroshock therapy is a blessing for most of them, the patients, their families, and their doctors have never really liked this form of treatment. There is something assaultive and violent about it, try as we do to improve our techniques of administering it.

There is surely something that goes awry in a patient's body chemistry in this strange illness. Some of my colleagues insist that it is psychogenic, that human beings worry and think themselves into melancholia. This becomes harder to accept as the continuing parade of these patients passes in review. We have been forced to invent words to hide our ignorance about the etiology of this disorder. We say that a great number of these cases are endogenous, that they come from within, which is another way of saying that something goes wrong in the chemical brew within us to produce these states. Here, if anywhere, is a challenge of the first magnitude for the neurochemists and the neuropharmacologists.

A word should also be said about the new attack on anxiety neurosis and on epilepsy. The advent of mephenesin in England some 10 years ago heralded the fact that drugs that were not sedative could lessen the symptoms of tension and jitteriness that engulf a patient sick with an anxiety reaction. Recently a mephenesin derivative, meprobamate,* has been made available to the clinician. Some of the early reports are most hopeful. If this drug or others like it will relieve anxiety symptoms, it will be used by general practitioners in one of every 4 or 5 patients, because this is one of the most common ills of man.

The researches of Merritt and Putnam that led to the introduction of Dilantin by Parke, Davis in 1937 have had an impact on a million and a half persons with epilepsy in this country and untold others throughout the civilized world. Like many

* The trade name of Wallace Laboratories for meprobamate is Miltown; the trade name of Wyeth, Inc. for meprobamate is Equanil.

of the drugs used in nervous system disorders, it has its drawbacks and its disappointments, but it was a monumental stride forward. Here is an example where the invention of a new pharmacologic tool opened up new therapeutic vistas. It arose out of the discovery by two Italians that fits could be induced in cats by passing an electric current through their heads. Merritt and Putnam tested the ability of 700 compounds to inhibit such fits, and Dilantin was the result. Here, again, is an example of the tenacity of the pharmaceutical industry. Dilantin was good, but not perfect. The continuing efforts of other companies—Sandoz with Mesantoin, Imperial Chemicals with Mysoline, Parke, Davis with Milontin, Lederle with Hibicon, and the long term effort of Abbott that has yielded Tridione, Paradione, Phenurone, Gemonil, and now Peganone—have converted the epileptic from a second class to a first class citizen in this country, permitting him to cast aside the stigma that had surrounded his illness since Biblical times. The story of epilepsy during the last 20 years is one of the most creditable achievements of the pharmaceutical industry.

The new pharmacologic attack in psychiatry and in neurology is imposing in its accomplishments in recent years. Much remains to be done; only a beginning has been made. The areas of ignorance are so vast that this is still a frontier. When all the psychotics and psychoneurotics and neurologic patients are grouped together, they constitute many more than half of the sick persons in this country. A look at Veterans Administration statistics will bear this out. A new land to break to the plow stretches beyond the horizon. These are rich unbroken fields and their potential harvests are tremendous.

Courses in Pediatrics

The following short courses will be conducted at The Children's Hospital of Philadelphia in May and June 1956.

1. *Pediatric Advances for Pediatricians and General Practitioners.* May 28 through June 1, 1956. A refresher course conducted by the Staff of the Children's Hospital of Philadelphia, in collaboration with the Department of Pediatrics of the University of Pennsylvania and the Camden Municipal Hospital. Tuition, $100.00.

2. *Practical Pediatric Hematology.* June 4, 5, and 6. Conducted by Dr. Irving J. Wolman and other members of the Hematology Department of the Children's Hospital, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $60.00.

3. *Blood Group Incompatibilities and Erythroblastosis Fetalis.* June 7 and 8. Conducted by Dr. Thomas R. Boggs, Jr., of the Philadelphia Serum Exchange of the Children's Hospital of Philadelphia, under the auspices of the Graduate School of Medicine, University of Pennsylvania. Tuition, $50.00.

For further information write to Irving J. Wolman, M.D., Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46.

Meprobamate

Its Pharmacologic Properties and Clinical Uses*

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NEW BRUNSWICK, N. J.

The recently introduced drugs, called ataraxics, that are used to alleviate certain symptoms of neuroses and psychoses can be divided into two broad classes. The first group, which has chlorpromazine and the Rauwolfia alkaloids as its most important representatives, is characterized by its important effects on the autonomic nervous system. The other, represented by meprobamate,† acts on the central nervous system only, without affecting autonomic functions. The present article describes briefly how meprobamate was developed, summarizes its pharmacologic actions, and outlines the clinical results that it has produced.

The Development of Meprobamate. The parent substance from which meprobamate was developed is mephenesin. Chemically, mephenesin is 3-*o*-toloxy-1,2-propanediol. It was introduced in 1946 as a muscle relaxant[2] and is widely used in a variety of conditions where muscle spasm is a factor.[5]

The greatest disadvantage of mephenesin is its short duration of action. After it was established that the evanescent action of the drug was due to the oxidation of mephenesin in the body to β-*o*-toloxy-lactic acid, which is physiologically inactive,[32] various related compounds were prepared in which blockage of the hydroxyl groups by various radicals made this method of detoxification inoperative.[4, 6] Unexpectedly, mephenesin carbamate and other related *o*-toloxypropyl carbamates did not possess a longer duration of action than mephenesin.[9] Meanwhile, it was also shown that certain 2, 2-disubstituted-1, 3-propanediols, while possessing pharmacologic properties similar to those of mephenesin, had in addition a particularly intense action at supraspinal levels.[3, 7] The dicarbamate derivatives of these compounds were long acting, although most of the substances had only a low order of activity.[8] Among these, 2-methyl-2-*n*-propyl-1, 3-propanediol dicarbamate, to which the generic name "meprobamate" was assigned, was unusual in possessing both pronounced muscle-relaxant and potent anticonvulsant properties and in exerting a marked taming effect on monkeys.[10, 11, 20, 21]

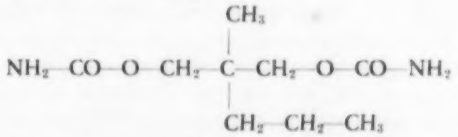
The Chemistry of Meprobamate. The compound was discovered in the Wallace Laboratories in 1950.[27] It is a white crystalline powder of characteristic bitter taste, melting without decomposition at 105 to 106 C. The solubility of meprobamate in water is low but it can readily be dissolved in most organic solvents. Meprobamate

* To the memory of my friend Lowell S. Selling who by his sound judgment, imagination, and enthusiasm was the first to recognize the merits of meprobamate in clinical practice. His premature death (on January 18, 1955) deprived him of the satisfaction of seeing the corroboration of his work.

† The trade name of Wallace Laboratories for meprobamate is Miltown; the trade name of Wyeth, Inc., for meprobamate is Equanil.

is stable in dilute acid and alkali and is not broken down at hydrogen ion concentrations occurring in gastric or intestinal juices.

The structural formula of the drug is as follows:



It is remarkable that a compound of such simple chemical structure should have such well-defined pharmacologic action. Meprobamate is one of the very few simple aliphatic compounds used in medicine, and its low toxicity may be the result of this simple structure. All other tranquilizers and central nervous system depressants possess in their molecules either ring structures (chlorpromazine, reserpine, azacyclonol, the barbiturates, methyprylon, glutethimide) or unsaturated linkages (methylparafynol, ethinamate, ethchlorvynol). The absence of a ring structure in the meprobamate molecule helps to explain the absence of habit-forming and addictive properties of the drug. The low incidence of side effects observed with meprobamate may be related to the absence of the highly reactive unsaturated linkages.

Pharmacologic Properties. Meprobamate has three pharmacologic properties of unusual interest; they are muscle-relaxant action, anticonvulsant action, and a taming effect best observed in monkeys.

The muscle-relaxant action is similar to that of mephenesin but of greater potency and longer duration. Only voluntary skeletal muscles are affected. The diaphragm is relatively insensitive to the action of meprobamate, and for this reason, respiration remains unimpaired even after administration of extremely large doses of the drug. Meprobamate is much more effective in reducing muscle spasm than normal proprioceptive muscle tension. Small doses will remove spasm and tremor experimentally produced by strychnine, neostigmine, and tetanus toxin, while much larger amounts are required to decrease normal muscle tension.[10–12]

Meprobamate has a strong anticonvulsant action and is particularly effective in protecting animals from convulsions and deaths caused by toxic doses of pentylenetetrazole. It possesses a very wide margin of safety. In mice, less than one tenth of a lethal dose of meprobamate protects from a lethal dose of pentylenetetrazole. Meprobamate is also very effective in protecting animals from death caused by strychnine. The antagonistic action of meprobamate against these chemical convulsants is superior to that of many barbiturates, mephenesin, and trimethadione because it is apparent in doses that given by themselves do not have sedative effects and do not affect the animals in any way. Meprobamate also effectively modifies electroshock seizures in animals.[10]

Meprobamate produces characteristic behavior changes that can best be observed in monkeys. After a suitable dose of meprobamate, the animals lose their fear, hostility, and aggressiveness and become tame and friendly. Appetite is unimpaired and full interest in the environment retained. The behavior of the meprobamate-treated animals differs strikingly from that displayed by monkeys receiving reserpine or chlorpromazine. After reserpine the animals, while tame and unaggressive, are

listless and catatonic. Monkeys receiving chlorpromazine also lose interest in their surroundings but remain suspicious and capable of attacking when handled or prodded.[10, 20]

The Site and Mode of Action. Meprobamate has a marked blocking action on interneurons. This action can be demonstrated at the level of the spinal cord by showing that the knee jerk, which has a reflex arc with no interneurons, is not affected by the drug, while the flexor reflex and the crossed extensor reflex, which have one or more interneurons interposed between the afferent and efferent arcs, are decreased or abolished.

The most striking property of meprobamate is its selective action on the thalamus. Electrical recordings taken from the thalamus show that meprobamate in low doses causes marked synchronization of activity which manifests itself by a slowing of frequency and a marked increase of voltage. The pattern is quite different from the spindling seen after barbiturate administration. Simultaneous recordings taken from the cerebral cortex and other subcortical structures are not affected in any way. Leads taken from the hypothalamus and the limbic area also remain unchanged. After larger doses, an increase in voltage in certain subcortical structures, particularly the caudate nucleus, also becomes apparent. Extremely large doses are required to produce changes in the cortical pattern.[20, 21, 29]

The selective action of meprobamate on the thalamus is a unique property of the drug. Other ataraxics, such as chlorpromazine and reserpine, do not cause such changes. It is of interest to speculate about the possible connections between selective changes in the thalamus and the effectiveness of the drug in psychoneurotic conditions. It may well be that one of the physiologic expressions of psychoneurosis consists of reverberation of discharges in the complicated interneuronal system of the thalamus. It is possible that the thalamic interneurons are especially sensitive to the action of meprobamate and that the blockage of some of these interneurons in the thalamus produces a synchronizing and normalizing effect on this structure.

Meprobamate does not seem to affect the autonomic nervous system. It does not change the responses of animals to acetylcholine, epinephrine, or histamine. In this respect the drug differs greatly from other ataraxics, which have potent adrenolytic, atropine-like, and antihistaminic action.

Toxicity. The acute toxicity of meprobamate in animals is very low. For instance, in mice the intraperitoneal administration of 800 mg./Kg. is required to produce death in 50 per cent of the animals. This figure indicates that meprobamate is about four or five times less toxic than most barbiturates. The chronic toxicity of the drug is also unusually low. Animals tolerate 1 per cent of the drug in their diet during their whole life span, and this does not significantly reduce their growth rate, resistance to infections or other unfavorable environmental stimuli, or fertility.

The low toxicity of the drug is further attested by the results in human beings who have taken large numbers of tablets in suicidal attempts. Five such cases have come to my notice. After 20 to 50 tablets, these patients became somnolent, but all recovered spontaneously within 48 hours and suffered no aftereffects. The use of analeptics other than hot coffee was not required.[26]

Fate in the Body. The results available up to the present indicate that approxi-

mately 10 per cent of the drug is excreted in the urine unchanged. The bulk of the remaining 90 per cent of the drug is apparently excreted as a conjugate with glucuronic acid. We have not succeeded in isolating the expected hydrolytic or oxidation breakdown products of meprobamate in the urine. A simple test to determine blood levels of meprobamate is not at present available.

CLINICAL USES

Every new drug passes through three stages before its clinical usefulness is established. During the first stage, it receives enthusiastic and often uncritical acceptance for a variety of conditions. Meprobamate appears at present to be in this stage. During the second phase, a reversal of judgment frequently occurs and the value of the drug is doubted by many. Eventually, during the last phase, the true clinical value of the product is established.

The numerous reports evaluating meprobamate in the treatment of anxiety and tension states and other manifestations of psychoneurosis, such as sleeplessness and tension headaches, suggest by their consensus of opinion that the drug may have real merit in the treatment of these conditions. The value of meprobamate as a muscle relaxant in rheumatic conditions also appears widely recognized. Clinical trials relating to the possible usefulness of the drug in the treatment of psychoses and of certain forms of epilepsy are in progress, but definite conclusions have not yet been reached.

THE PSYCHONEUROSES

The psychoneuroses constitute an ill defined disease entity that can manifest itself by a variety of symptoms. Instead of following a formal classification system, it appears preferable to discuss the effects of meprobamate under the diagnostic headings widely used by physicians.

Anxiety and Tension States. Meprobamate has been found uniformly successful by all investigators using the drug in these conditions.[13–15, 19, 22, 23, 25, 30, 35, 36, 42] It has been reported of assistance in controlling the irrational fears and vague sense of dread characteristic of the anxiety state, in relaxing the associated bodily tensions, in lessening irritability, and in improving the ability to concentrate. Unsociable patients again became able to take part in the life of the community. Many lost their morbid preoccupation with their symptoms and were able to resume the efficient pursuit of their careers. Patients also became much more accessible to psychotherapy. The drug increased their confidence in the physician and often enabled them to loosen their emotional defenses.

The incidence of improvements and recoveries described by various authors varies between 70 per cent and 95 per cent of cases. Improvement in the patient's condition, as a rule, could be observed within the first few days of treatment. Almost immediate results could be seen in treatment of agitation in anxiety states. With some patients, treatment had to be continued for three to four months before full improvement could be obtained.

The favorable results obtained with meprobamate appear to be objectively de-

monstrable and not due to suggestion. Selling[26] found that patients given placebos after a period of meprobamate treatment complained about the return of their symptoms in every case. Hollister et al,[22] using a double-blind technique, had no difficulty in differentiating between true and placebo effects. Of 17 patients, 11 improved only after meprobamate, whereas only 3 improved after placebo alone. In 3 instances improvements were noted after both the placebo and meprobamate. Dickel et al[14] devised an electromyographic test to measure ability to relax muscle tension. They found that meprobamate produced a definitely increased ability to relax on command and a marked improvement in the patient's general coordination. These changes were correlated with the improvements in emotional response observed in the same patients.

Meprobamate appears to be more effective for the treatment of anxiety and tension than barbiturates or mephenesin. Borrus[13] obtained excellent results in 67 patients with anxiety reactions who had previously failed to respond to barbiturates and mephenesin. Similar results were reported by Lemere[25] and Selling.[25, 26] Hollister et al,[22] using a double-blind technique, found meprobamate of a similar effectiveness in relieving symptoms of anxiety reactions as reserpine and as the alseroxylon fraction of Rauwolfia. Phenobarbital proved much less effective than meprobamate or reserpine in this study. Hollister concluded that meprobamate, because of its effectiveness and lack of side reactions, was the most generally useful medication in the treatment of anxious patients.

Osinski[20] studied a group of 113 hospital outpatients suffering from anxiety reactions, many of them having proved refractory to previous treatment with barbiturates or to a combination of barbiturates and other ataraxics. There were 40 patients who had been unresponsive to such previous treatment, and of these 70 per cent showed good or very good response to meprobamate.

Lemere[25] compared chlorpromazine and reserpine with meprobamate. In his experience, the results with chlorpromazine and reserpine in office practice were much less spectacular than those reported following use of these drugs with severely disturbed patients in state hospitals. Lemere considers meprobamate, which he used in over 250 patients in his general psychiatric practice, to be the drug of choice for the relief of tension and anxiety.

Tension Headaches. In tense and anxious people, adverse life situations often give rise to sustained contractions of the posterior muscles of the head and neck which secondarily produce pain in the head, neck, and shoulders. This most common type of headache, sometimes also called psychosomatic or nuchal headache, is in reality only a manifestation of psychoneurosis in which the symptom of headache predominates. For this reason, the effectiveness of meprobamate in this condition is not unexpected. The drug may be of particular value in this condition not only because of its action on psychoneurotic symptoms, but also because of its relaxant action on skeletal muscles.

Selling[25, 26] observed that the most dramatic reports of recovery in patients given meprobamate came from cases where tension headache was the chief complaint. Of 27 patients with this complaint, 23 either recovered or reported sufficient improvement so that they were no longer concerned with this symptom. Meprobamate has

also been found of value in the treatment of vascular headache. The drug can be administered to hypertensives with safety because it does not affect the blood pressure.[12] The effect of meprobamate on migraine has not been studied.

Patients receiving electroshock treatment usually develop headache within an hour following treatment. Thal[40] reported that the administration of a single tablet of meprobamate one hour prior to giving the electroshock prevented the occurrence of the headache in every instance. (In this study, 120 female psychotic patients were observed.)

Insomnia. All sedatives and hypnotics when administered to human beings in appropriate clinical dosage produce a characteristic sleep pattern in the electroencephalogram. Meprobamate, in common with other ataraxics such as chlorpromazine and reserpine, does not produce such changes. Sleep patterns after meprobamate have not been observed even after administration of large doses to human beings. (A healthy male subject of 31 years took 8 tablets within one hour; there were no changes in his electroencephalogram.) Thus, it would be incorrect to call meprobamate a hypnotic. This observation notwithstanding, the drug has been found of considerable value for the induction of sleep, probably through relaxing the anxieties and tensions that prevent its natural onset.

Sleep following meprobamate differs in several respects from that following the administration of barbiturates. After barbiturates, unconsciousness sets in suddenly. After meprobamate, on the other hand, the patient is able to lie quietly without worrying until he drifts into sleep. Patients can be readily wakened. Sleep is usually dreamless and restful and is not followed by a "dopey" feeling on awakening.

Selling[35, 38] found it possible to produce sleep with meprobamate in every case except in patients suffering from true psychotic depression, and was able to discontinue entirely the use of barbiturates or similar somnifacients in his practice. While meprobamate proved of particular value in enabling the patient to fall asleep, many patients awakening early in the morning were enabled to return to sleep by taking a supplementary dose of meprobamate during the night.

Mulinos et al[28] evaluated meprobamate in 26 hospital patients all of whom had previously been taking a hypnotic (usually pentobarbital). They found that 87 per cent slept well after meprobamate as compared with 46 per cent after a placebo. In another study, Mulinos et al,[28] using meprobamate with 106 hospitalized patients, also reported it to be an effective hypnotic. Under placebo, only 7 per cent of his patients slept well, whereas 64 per cent did so under meprobamate. Doses as large as 1 Gm. (2½ tablets) taken at night caused no hang-over or other aftereffects.

Lasagna,[24] in a double-blind study carried out on 46 chronically ill hospitalized patients troubled with insomnia, compared meprobamate with four hypnotics. He found that meprobamate had about the same order of hypnotic effectiveness as phenobarbital, both as to time of onset and duration of effect. He also observed that a dose of 800 mg. was not appreciably more effective than one of 400 mg. except that the duration of sleep was usually somewhat increased at the higher dose.

Grinker[19] and Borrus[12] have both observed that when meprobamate is used as a tranquilizer during the day, patients so treated will often require no additional seda-

tive to produce sleep at night. This effect was noted particularly in agitated patients suffering from anxiety states and depression.

Lemere[25] feels that meprobamate is the drug of choice in the treatment of insomnia in ambulatory office patients. Alcoholics in the withdrawal phase have also been reported as obtaining restful sleep after meprobamate. In this respect, meprobamate appeared far superior to barbiturates and other types of hypnotic drugs.[29]

Alcoholism. In the treatment of alcoholism, meprobamate helps to control withdrawal symptoms during the sobering-up phase.[17, 29, 41, 42] After withdrawal has been accomplished, the drug facilitates adjustment to life without alcohol.[13, 17, 41, 42] It has not been found to be habit forming.[13, 25, 26]

The persistence of anxiety, tension, and insomnia in alcoholics even after they have abstained from alcoholic beverages for considerable periods of time makes the frequency of relapses understandable. In these patients, meprobamate alleviates tension, restlessness, and insomnia and appears in these respects much superior to barbiturates and other hypnotics.[29, 42]

Thimann[41] found meprobamate to be a safe, rapid, and effective sedative for the subacute stage of withdrawal from alcohol. Severely intoxicated subjects were initially treated with paraldehyde or chloral hydrate during the acute stage, and were transferred to meprobamate only one or two days after admission. In cases of mild intoxication, meprobamate could be administered immediately upon admission. O'Hollaren[29] also believes that meprobamate is of little value in the severely intoxicated patient and that the usefulness of the drug lies chiefly in enabling the patient to control his tenseness and irritability during abstinence from alcoholic beverages. In the control of tremor, meprobamate proved very effective and definitely superior to mephenesin.

Fox[17] evaluated meprobamate as well as a number of other drugs in acutely intoxicated patients admitted to a private hospital. Meprobamate used alone and in low dosage did not control violently agitated patients. In larger doses (about 2 tablets four times a day), and particularly when given in conjunction with small doses of chlorpromazine, meprobamate produced results that were much superior to those obtained with any other therapeutic regimen previously tried. Patients so treated commented that they felt better at the termination of treatment, and their period of hospitalization could be shortened. Barbiturates were not needed during the withdrawal period.

Psychosomatic Symptoms. Meprobamate has proved of value in a variety of conditions of psychosomatic origin.

Pain. Gastric pain of psychosomatic origin responded well to meprobamate, but pain due to ulcer was not relieved.[26] Kessler and Barnard[23] found meprobamate useful in the control of somatic pain accompanying neoplastic disease. It is unlikely that the drug could have affected the threshold to pain perception directly, as pharmacologic tests in animals did not show the drug to have an analgesic action. However, it is possible that by lessening the patient's anxiety, meprobamate may have increased his tolerance to pain.

Neurodermatitis. Selling[26] and others[12] reported that meprobamate cleared up

skin rashes of psychosomatic origin. Sokoloff[28] found the drug of considerable value as an adjunct in the treatment of idiopathic anogenital pruritus.

Menstrual Stress. In some women, symptoms of anxiety and tension appear only shortly before and during their menstrual periods. In these patients, meprobamate is often of great value in reducing irritability, pressure, headache, and general discomfort.[26] Pennington[31] and Dixon[15] also reported on the value of meprobamate in premenstrual tension and dysmenorrhea.

Behavior Problems. Selling[25, 26] reported on 10 tense and restless children who presented behavior problems. Of these, 7 benefited by meprobamate treatment. The drug helped them to quiet down and to concentrate better. In Perlstein's[32] series of 29 very serious behavior problems (including 7 psychotics), only 7 showed benefit from meprobamate.

PSYCHOSES

Up to the present, the result of only one study relating to the value of meprobamate in hospitalized psychotic patients has become available. Pennington,[31] at the Mississippi State Hospital, compared the effectiveness of meprobamate, reserpine, chlorpromazine, azacyclonol, pipradrol hydrochloride, and whole root Rauwolfia in 1250 patients in a study extending over 18 months. Most of the patients were schizophrenics. According to her report, the results obtained with meprobamate were quite similar to those obtained by her and other investigators with chlorpromazine and reserpine. About 3 per cent of the patients were completely rehabilitated. Improvement was marked in an additional 29 per cent, and moderate in 50 per cent of the patients. The remaining 18 per cent were not influenced.

To achieve these results, higher dosage than that used in the treatment of psychoneuroses was needed. A few patients required as many as 12 tablets twice daily. Most received about 3 to 4 tablets twice daily. Under this regimen, sleep was improved, appetite increased, and psychotic delusional trends were often dispelled. Some belligerent patients who formerly had required several shock treatments a month for control became calm and could be kept with other patients while taking the drug.

Borrus[13] and Selling[25, 26] evaluated meprobamate in a few ambulatory schizophrenics who were making marginal adjustments. Of 12 of these patients, 6 showed some improvement, mainly of better social adjustment, after meprobamate.

Manic-depressives and hypomanics who were obviously disturbed but not committably psychotic were also favorably affected by meprobamate.[26] There are usually difficulties in getting these patients to take the medication because they do not believe themselves to be sick. Many of them were able to keep out of trouble as long as they took the drug.[26]

Available evidence does not indicate that meprobamate is of value with patients suffering from psychotic depression.[26] Because of the suicidal tendencies of these patients, it is of great importance to keep them under close supervision and to differentiate their condition from that presented by the anxiety reactions. Such a diagnosis is often difficult to make.

Several investigators have reported that reserpine sometimes causes depression and

suicidal tendencies in certain subjects. Meprobamate has not been known to elicit suicidal tendencies, nor to aggravate these tendencies when present.[12, 25, 35]

Electroshock treatment is no contraindication to the administration of meprobamate. Selling[36] observed that meprobamate is often of value for the control of postshock confusion. Thal,[40] in a well controlled study of 120 psychotic patients, observed the effect of meprobamate premedication on electroshock treatment. One 400 mg. tablet was given one hour before electroshock. Under premedication, the patients were less apprehensive, experienced less postshock confusion, and regained full consciousness more rapidly than patients not receiving the drug. Postshock headache did not occur. The convulsive response to electroshock itself was only slightly altered. The tonic phase was perhaps slightly less intense in onset, while the duration of the clonic phase was slightly shortened.

EPILEPSY

The strong anticonvulsive action of meprobamate in animals made the evaluation of the drug in various forms of epilepsy of great interest.

Meprobamate appears to be of no value in the treatment of grand mal. Thirty-one cases not responding to other anticonvulsants were treated during an eight month period with up to 8 tablets of meprobamate per day.[17a] The drug proved ineffective. Perlstein[32] found that meprobamate, like trimethadione and other anticonvulsants useful in petit mal, sometimes precipitated grand mal spells in patients subject to both grand mal and petit mal spells.

Perlstein[32] stated that meprobamate is of considerable value in the treatment of idiopathic petit mal seizures. Although not as effective as trimethadione, it seemed to be at least as effective as paramethadione and all other anti-petit mal drugs. It has the advantage over trimethadione and paramethadione in being relatively nontoxic. The drug appeared markedly more effective in idiopathic petit mal seizures, where 83 per cent (of 18 cases) were benefited, than in organic petit mal, where only 22 per cent (of 53 cases) were helped. Livingston[26] reported favorable results in some cases of minor motor (akinetic and massive myoclonic) seizures in children who as a rule were also mentally retarded.

MUSCLE SPASM

Meprobamate shows a muscle-relaxant action on skeletal muscle similar to that of mephenesin but of greater intensity and longer duration. For this reason, one would expect the drug to be of value in conditions where muscle spasm is a factor, such as in various rheumatic conditions, poliomyelitis, spasticity due to upper motor neuron lesions, cerebral palsy, and related conditions.

Chronic Rheumatic Conditions. Smith[37] evaluated meprobamate in over 100 cases of chronic rheumatic conditions. He found that fibrositic symptoms were greatly improved in those cases where muscle spasm predominated. Some of the conditions successfully treated with meprobamate were: rheumatoid spondylitis, cervical myositis (wry neck), and acute and chronic low back strain. The drug was found completely ineffective in true rheumatoid arthritis.

Eisenberg and Neviaser[16] evaluated meprobamate in 107 patients presenting a wide variety of conditions involving muscle spasm, pain and tenderness, restriction of motion, and spinal tilt. About 90 per cent of the patients were significantly improved, 65 per cent showing marked improvement or complete recovery. Relief was greatest in acute and chronic low back strain, cervical myositis, and various osteoarthritic conditions. Symptoms caused by ruptured intervertebral discs and by postoperative conditions appeared to respond less well to treatment. The authors concluded that meprobamate is in all respects greatly superior to mephenesin. They believe that it is the best muscle relaxant available for the symptomatic treatment of acute and chronic low back strain, cervical myositis, and certain osteoarthritic conditions.

Cerebral Palsy. Scheslinger[24] evaluated the effect of meprobamate on 39 patients, all of whom took the drug for well over a year. He reports an enhancement of motor effort and reduction of involuntary movements of a greater degree than with any other drug including all the mephenesin analogues. Meprobamate dampens activity sufficiently to allow corrective therapy and motor training. Its use appears particularly worth while in the athetoid and dyskinetic patients.

In Perlstein's[22] series, meprobamate showed some effectiveness in 10 of 44 patients suffering from cerebral palsy. The most responsive cases were the athetoids where three marked and five moderate responses were obtained among 26 cases. Patients with pyramidal tract involvement were not often helped. These results have, in general, been confirmed by Baird.[1] Gillette[18] observed a very definite reduction of tension in both spastic and athetoid patients. This change was not referable to better emotional control as most of these patients were too young to present emotional problems. About three days after treatment was instituted, the application of braces became easier, speech improved, movement could be carried out with greater speed and ease, and the involuntary movements decreased.

Various Neurologic Conditions. Occasional cases of hemiplegia and paraplegia have shown a decrease in flexor spasm, but clinically useful improvement is obtained in only a few cases.[12] Painful muscle spasm in acute poliomyelitis has been effectively relieved with meprobamate without producing any respiratory embarrassment.[15] Multiple sclerosis and parkinsonism have proved unresponsive to meprobamate treatment.[12] In many of these patients, however, meprobamate produced restful sleep.

DOSAGE AND SIDE EFFECTS

The dosage used by most investigators is one or two 400 mg. tablets three times a day. For sleep, 2 tablets about 30 minutes before retiring are usually taken. With seriously disturbed psychotics, much larger doses may be required. Extensive clinical investigations have shown meprobamate to be a drug of extremely low toxicity. Patients receiving 1 or 2 Gm. of meprobamate daily for over 12 months showed no evidence of systemic toxicity.[24] A few patients, given up to 4 Gm. per day, and followed for six months, also showed no evidence of toxic effect.[17a] Blood dyscrasias, urinary changes, or liver damage attributable to its use have not been observed.

The only side effect reported with any frequency is drowsiness. The incidence of drowsiness appears to vary greatly in the different series reported. It is more likely to occur after 2 tablets three times a day than after 1 tablet three times a day. Perlstein believes that adults are less susceptible to drowsiness at higher doses than children. Some patients who complain of drowsiness when first taking the drug may lose this symptom after continued administration for a week or so. Drowsiness can often be controlled by reducing the dose. If this is undesirable, the concomitant use of amphetamine usually counteracts any drowsiness due to meprobamate administration.

The only serious side effect reported after meprobamate up to the present is allergic reaction.[25, 26] This response develops, as a rule, in patients who have had only one to four doses of meprobamate and have not had previous contact with the drug. In mild reactions of this type, there is an itchy urticarial or erythematous rash, which may be generalized or confined to the groins. More severe cases may also have fever, fainting spells, angioneurotic edema, and bronchial spasm.

Treatment consists of the administration of epinephrine, antihistamines, and possibly also hydrocortisone. Meprobamate should be stopped and no further attempt made to use this medication.

Certain patients have complained of gastric discomfort after taking meprobamate. Because the incidence of this common complaint was noted to be similar after the drug as after a placebo (when a double-blind technique was used), it appears unlikely to be of any consequence.[12]

SUMMARY

Meprobamate is a new tranquilizer with muscle-relaxant properties. It differs from other tranquilizing drugs both in the simplicity of its chemical structure and in its mode of action. Meprobamate has a selective action on the thalamus and a blocking action on spinal interneurons. The drug does not affect autonomic functions.

Meprobamate has proved to be of particular value in anxiety and tension states and in related conditions such as tension headache, sleeplessness, and menstrual stress. The muscle-relaxant properties of the drug are of value in the treatment of cervical myositis, acute and chronic low back strain, various osteoarthritic conditions, and cerebral palsy. The drug has also been used in the treatment of psychotics and in certain cases of petit mal epilepsy, but its value in these conditions has not yet been established.

Side effects with meprobamate occur rarely. Some patients complain of drowsiness when first put on the drug, but this often passes away in a week or so if the medication is continued. A few cases of allergic skin reactions have occurred, but no cases of blood changes or liver or kidney damage have been reported. The drug appears to be nonaddictive and non-habit forming. It can be used with patients undergoing electroshock treatment and does not precipitate depression.

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International Symposium on Chlorpromazine

Part I

(*in the January-March issue*)

"The Challenge of Bio- and Chemotherapy in Psychiatry" *by Félix Martí-Ibáñez, Arthur M. Sackler, Mortimer D. Sackler, and Raymond R. Sackler;* "Chlorpromazine and Neuroleptic Treatments in Psychiatry" *by Jean Delay and Pierre Deniker;* "Pharmacodynamic Basis for the Use of Chlorpromazine in Psychiatry" *by Simone Courvoisier;* "Treatment of Mental Disorders with Chlorpromazine" *by P. Kielholz and F. Labhardt;* "Chlorpromazine Treatment of Hospitalized Psychotic Patients" *by Douglas Goldman;* "Ambulatory Treatment with Chlorpromazine" *by J. Sigwald, D. Boutlier, and P. Nicolas-Charles;* "Incidents and Accidents in Chlorpromazine Therapy" *by Barahona Fernandes and Gonçalves Leitão.*

Part II

(*in the April-June issue*)

"Neurophysiologic Activity of Chlorpromazine in Clinical Use" *by H. E. Lehmann;* "17-Hydrocorticosteroid Levels in the Peripheral Blood of Psychotic Patients under Treatment with Chlorpromazine and Reserpine" *by Co Tui et al;* "Some Interesting Pharmacodynamic Properties of Chlorpromazine" *by Erwin Lear and Albert E. Chiron;* "The Location of Action of Chlorpromazine in the Central Nervous System" *by Mirko Carreras and Franco Angeleri;* "Clinical Evaluation of Chlorpromazine Therapy for Mental Illnesses" *by Paul E. Feldman;* "Sleep Therapy and the Use of Chlorpromazine" *by Henri Ey and Henri Faure;* "Comparative Psychopathology of Shock Therapy and Pharmacotherapy" *by Klaus Hartmann et al;* "Undesirable Effects and Clinical Toxicity of Chlorpromazine" *by Irvin M. Cohen;* "Some Considerations on the Use of Chlorpromazine in a Child Psychiatry Clinic" *by Herbert Freed and Charles A. Peifer, Jr.;* "Psychologic Changes in Man after Chlorpromazine and Certain Types of Brain Surgery" *by Asenath Petrie and Jacques Le Beau;* "Clinical Research on Chlorpromazine and Reserpine: A Comparative Review of the Clinical Problems in State and Private Psychiatric Hospitals" *by John Donnelly and William Zeller;* "Summation and New Perspectives on Bio- and Chemotherapy in Psychiatry" *by Arthur M. Sackler, Mortimer D. Sackler, Raymond R. Sackler, and Félix Martí-Ibáñez;* "Fatal Hyperpyrexia During Chlorpromazine Therapy" (*Clinical Psychopathologic Conference*) *by Frank J. Ayd, Jr.*

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Chlorpromazine in General Practice

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ST. PAUL, MINN.

To attempt to add one more article to the already extensive medical literature concerning the use of chlorpromazine (Thorazine*) in the various fields of medicine seems almost, on first glance, superfluous. However, in the present paper I will try to deviate somewhat from the previous articles in that this article is primarily concerned with the use of chlorpromazine in the care of patients seen daily in general practice. No attempt will be made to give a statistical approach on the cure or benefits to various patients because, in the busy everyday practice of medicine at the bedside, in the home, and in the hospital, a statistical approach becomes almost impossible. There are numerous articles that were written recently with excellent statistical data on the good and bad points of the use of chlorpromazine in a great many neuropsychiatric disorders and of its use in surgery, obstetrics, pediatrics, dermatology, and various other fields of medicine; in most of these a statistical approach has been well carried out. This report, then, will be concerned primarily with the general impressions gained by a general practitioner on the effect of chlorpromazine on patients treated on both an out- and inpatient basis over a period of approximately 15 months.

In my particular practice, chlorpromazine has been used in approximately 1600 patients varying in age from 3 months to the oldest, now 98 years of age. Therapy in these cases has ranged from several doses of the drug, in some cases of nausea and vomiting in infancy and associated with gastroenteritis, up to several patients who have now been on the drug for as long as 11 to 12 months. At the present time approximately 56 patients have been taking the drug longer than three months, about 30 have now been on the drug for approximately nine months, and 5 patients have been on chlorpromazine for 11 to 12 months.

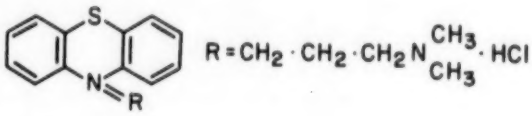
In my practice there is no restriction on any one field of medicine; I have not at the present time limited my practice to the exclusion of surgery or obstetrics as some busy general practitioners can, but care for all patients seen. I have had occasion to use chlorpromazine in a wide variety of disorders; in fact, some of these disorders upon which the drug has been used have received but little mention in the literature. Insofar as the use of chlorpromazine in obstetric patients is concerned, I had occasion to use it in approximately 10 obstetric deliveries prior to reading the first article in the literature on its use in obstetrics. It was early and easily apparent that its ataraxic and antiemetic effect was very desirable in the woman in labor.

PHARMACOLOGY AND MODE OF ACTION

Chlorpromazine is primarily a central nervous system depressant, an agent that has been used for the control of nausea and vomiting. The drug was originally

* The trade name of Smith, Kline & French Laboratories for chlorpromazine is Thorazine

developed in France in 1951 by the Rhône-Poulenc Specia Laboratories and marketed by them under the trade name of Largactil (RP4560). The drug was synthesized during a search for phenothiazine derivatives similar to promethazine (Phenergan) that could be useful in clinical anesthesia. The actual chemical name is 10-(3-dimethylpropylamine)-2-chlorphenothiazine hydrochloride.



Following its discovery, the marked adrenolytic effect at the periphery was noted with chlorpromazine. It was also noted that the drug had a rather marked depressant effect that appeared to be primarily central in activity, questionably at the level of the hypothalamus or on the reticular activating system. Much experimental work has been done on chlorpromazine in attempting to elicit its specific action on the central nervous system. It is felt that chlorpromazine suppresses the neurohypophysis-adrenal connection at the level of the hypothalamus, which may account for its effect in inhibiting reaction to stress phenomena. It is therefore said to "alter the organism's ability to respond to external aggressions."

Laborit pioneered the use of chlorpromazine in France as a portion of his "lytic cocktail," used primarily for "artificial hibernation anesthesia" in the surgical treatment of elderly patients. This achieved a fair degree of popularity in France. From France this technique found its way to the rest of the continent and eventually to the United States, where it has been used in major cardiovascular surgery primarily. At the present time much research and clinical study is being done on the use of chlorpromazine in the various aspects of medicine, and innumerable papers are appearing, all of which seem to conclude that the drug has been of inestimable value in the general care of a large number of patients.

In attempting to describe the use of chlorpromazine in general practice, it is difficult to group patients and their symptoms into any specific category for descriptive purposes. However, to achieve some degree of orderliness in illustrating the various fields of medicine in which chlorpromazine has been of beneficial use, I will attempt to split the entire field of medicine into various categories in order to describe the use of the drug in each of these particular branches. Of necessity, the descriptions will be brief and in some instances almost cursory. In attempting to describe the use of a drug in an untold number of situations, adequate descriptions would require a volume and not a short paper.

NEUROPSYCHIATRY

First and foremost is the psychiatric field of medicine in which chlorpromazine has received its greatest popularity in America. It has been found to be useful in the treatment of both psychotic and neurotic syndromes and has become one of the outstanding drugs in the armamentarium of psychiatrists throughout this country.

Its use in acute and chronic anxiety states appears to be the most important field of usefulness insofar as general practice is concerned. The majority of patients seen in practice, no matter what the initial complaint is, appear to be suffering from chronic anxiety or an acute agitated anxiety, either on the basis of the effect of their illness on their daily living or the effect of their illness on their financial security. Therefore, agitation and anxiety become major factors even in the treatment of many minor physical disturbances. Those cases that have responded best to the use of chlorpromazine are cases marked by (1) agitation, (2) anxiety, and/or (3) aggression. Many patients exhibiting somatic symptoms on the basis of anxiety states, such as those of paroxysmal heart pain, tension headaches, irritable bowel syndrome with intermittent constipation and abdominal cramping, in which no organic disease can be found, and tension states with paroxysmal epigastric distress and various other somatic symptoms appear to respond very well to the administration of chlorpromazine. Most of these patients have been treated on an outpatient basis, and the results have been very satisfactory. In treating such disorders it must be emphasized that dosage in the patient is highly individualized, some patients being adequately controlled on as little as 20 to 30 mg./day, others requiring dosages up to 200, 300, or even 400 mg./day. In each patient dosage must be begun at a low level and gradually increased at a rate depending on the state of tolerance of the patient.

In the treatment of some of the severely agitated behavior disorders in children, as in the hyperkinetic child, chlorpromazine has been found to be extremely effective in retarding activity and in making the child much more aware of his own ability to control more adequately aggressive behavior. In the treatment of approximately 5 children in whom an aggressive type of behavior was apparent, good results were obtained in all cases, the children being adequately controlled with little or no untoward effects. However, in the treatment of such cases, a dosage somewhat greater than that ordinarily recommended for the treatment of children has been required, and on the basis of dosage per kilogram, approximately 2 to 3 mg./Kg./24 hours appears to be well tolerated and highly effective. Side effects have been minimal in these children, the most common side effects being subjective fatigue and drowsiness. However, in view of the previous behavior of such children, such side effects do not appear to be at all undesirable.

In the treatment of agitated depression, especially the menopausal and involutional melancholia that are so frequently seen, chlorpromazine has been a very effective adjunct in achieving a sense of well-being. There has been marked diminution in the degree of agitation, patients have complained much less of insomnia, and the obsessive-compulsive type of behavior frequently seen in involutional states has been markedly diminished. Insofar as relief of the depression is concerned, chlorpromazine has been much less effective, and psychotherapy in conjunction with the use of moderately stimulating drugs has been necessary for the relief of the pure depression state.

In the treatment of the agitated depressions of the menopause, hormonal therapy usually has been found to be necessary for relief of the migratory arthralgia, hot flashes, and vague abdominal discomfort that seem to accompany the menopause in a large number of patients. However, it has been noted that with adequate doses of

chlorpromazine given orally, the usual doses of estrogen that had been given previously have been reduced by almost half, with an increased sense of well-being. On occasion, using chlorpromazine and assurance alone, hot flashes have subsided considerably.

In my particular practice the opportunity to treat alcoholics has been very limited and therefore experience in only a few cases can be noted. In the treatment of the acute alcoholic, chlorpromazine was extremely effective, although its dosage must be watched closely and the patient observed very frequently during administration. Chlorpromazine appears to potentiate the central depressant effect of alcohol, and therefore administration must be begun cautiously. The ability of chlorpromazine to induce relaxation, to produce sleep without the usual stupor noted in acute alcoholism, and to control vomiting has been remarkable. Since the advent of intramuscular chlorpromazine for the treatment of acute alcoholism, it has been virtually unnecessary to resort to restraints for the control of alcoholic patients. Sufficient sedation is given so that the patient may be aroused when shaken but as soon as he is left undisturbed for a few moments, he falls back into a moderately deep slumber that appears to resemble natural sleep in all respects. This may last from 3 to 12 hours, after which the patient usually rouses feeling quite well and without the usual lethargic or nervous feeling that so commonly follows the use of barbiturates in the control of restlessness. I have had no opportunity to use chlorpromazine in the treatment of chronic alcoholism and therefore its use will not be discussed here.

In the treatment of intermittent insomnia due to psychic stress or agitation from any cause, chlorpromazine appears to be a highly effective medication which may induce sleep with a single dose given at bedtime without producing the marked hang-over effect so frequently noted with administration of the large amounts of barbiturates that are necessary to produce sleep in such agitated patients. In the treatment of intermittent insomnia occurring in a patient who during the day appears to be moderately well adjusted and without agitation, only a single dose of 25 to 50 mg. is given at bedtime, and on this regime an adequate and restful sleep can be obtained in most instances.

I have had occasion to use chlorpromazine in 4 cases of acute psychosis. One was a postpartum psychosis occurring a week after a normal delivery in a previously shy, rather withdrawn woman. Two other cases were women with paranoid schizophrenia with marked agitation. All patients were hospitalized and treated with intramuscular chlorpromazine in rather large doses, the daily dose averaging 600 mg. daily. In 1 patient, 1000 mg. daily was administered for three days in order to control the extreme agitation. From the treatment of these and other severely ill neurotic patients it has been my impression that patients requiring more than 300 to 400 mg. of chlorpromazine daily to control symptoms must eventually be institutionalized for major psychiatric treatment. Therefore, when doses of more than 300 mg. of chlorpromazine are required for sedation of agitated patients, it is mandatory that psychiatric consultation be sought.

NEUROLOGY

In the treatment of neurologic disorders chlorpromazine has been used in approxi-

mately 60 persons with an over-all effect that I have found extremely gratifying. Some attempt will be made to cover some of these syndromes that may fall under the care of the general practitioner.

Chlorpromazine has been used in the treatment of both Sydenham's chorea and Huntington's chorea in only a very few patients and has been remarkable in controlling the restlessness, nervousness, and agitation seen so frequently in patients with choreiform manifestations. By apparently controlling the restlessness and emotional stress under which these patients seem to live, the drug appears to improve the general clinical picture markedly. Although there is no objective evidence of its effect in subduing choreiform activity, nevertheless its effect in tranquilizing these suffering individuals is in itself a blessing. Dosage in these conditions must be individualized, and it is best in most instances to begin with a moderately low dose and gradually increase it. The usual beginning dose is approximately 10 mg. three or four times daily, gradually increasing by 20 to 30 mg. every other day until a satisfactory dosage level is obtained.

Chlorpromazine has been used with a moderate degree of success in approximately 5 children exhibiting cerebral palsy in its various forms. Three of these children are mentally deficient. The children in general tended to show increased relaxation and a markedly lessened anxiety, appeared more content, less irritable, and were much easier to manage. In several cases in which athetosis was apparent in association with cerebral palsy, there seemed to be moderate diminution of the athetotic movements. In general, improvement was judged by the remarks of the parents that these children appeared to be much easier to live with than previously.

Chlorpromazine has been used effectively in 2 cases of parkinsonism in association with other drugs that the patients had been maintained on previously. In both cases there appeared to be a moderate diminution in the tremor, although rigidity appeared to be unaffected. However, in general, both of these patients had been markedly anxious and somewhat irritable prior to the administration of chlorpromazine, and this appeared to lessen greatly after the achievement of a satisfactory dosage level. The patients became less withdrawn and appeared to be much happier while being maintained on adequate doses of chlorpromazine. One patient, who previously had remained almost continually at home, has now resumed employment and appears to be much more satisfied with his present condition.

Chlorpromazine has been used in the treatment of approximately 8 children with idiopathic convulsive seizures with a remarkable degree of effectiveness. These children characteristically suffer from irritability, hostility, and marked aggressiveness, which seem to be an inherent part of the epileptic personality. Chlorpromazine has produced rather dramatic results in relieving many of the mental and emotional strains in these patients. It has made them more agreeable, less aggressive, and much less irritable. They have become quieter, easier to manage, and much more cooperative in therapy. However, in this respect chlorpromazine has had no effect in lessening either the number or the intensity of convulsive seizures and seems to have no potentiating effect on anticonvulsant medication. Therefore, when chlorpromazine is used in such patients, the anticonvulsant medication must be continued at its previous dosage level.

Chlorpromazine has been used in numerous other neurologic entities, including craniocerebral trauma and postconcussion headaches, Ménière's syndrome, migraine headaches unresponsive to other therapy, multiple sclerosis, neuralgias (including atypical facial pain and tic douloureux), and 1 case of polyneuritis of pregnancy. In most cases it has served admirably to relieve the anxiety attending these illnesses and in many instances has helped to relieve many of the organic symptoms.

In acute head injury, restlessness and pain may be relieved with chlorpromazine without the depressant effect of opiates. Blood pressure in such instances must be observed closely to ward off the drug's hypotensive effects. In the treatment of post-traumatic headache in which no evidence of organic neurologic disease can be found, its use has resulted in a marked diminution in the intensity and frequency of headaches.

INTERNAL MEDICINE

Chlorpromazine has been remarkably effective in the treatment of many of the vascular diseases and tension states commonly seen in patients in the field of internal medicine. It has been used in a large number of cases of hypertensive cardiovascular disease, cerebral vascular accidents, coronary occlusions, and hypertension with extremely satisfactory results in relieving the apprehension and tension that appear to go with these particular entities. In hypertension many of the various complaints that a patient will enumerate appear to have no significant basis as regards the blood pressure. The headache, the dizzy spells, palpitation—all seem to be more related to a chronic tension state than to the disease itself, as has well been revealed in previous studies in which it has been shown that patients who know that their blood pressure is elevated will tend to have many more symptoms than will those in whom no knowledge of hypertension exists.

In the treatment of hypertension, chlorpromazine has been used in conjunction with the Rauwolfia derivatives, and such a combination has been found to be much more effective than the use of either product alone. Using Rauwolfia derivative alone, it has been noted that a satisfactory level of reduction of blood pressure is not attained until two to four weeks or more has elapsed. However, with the combination, a reduction in blood pressure has been apparent in as little as four to five days of therapy. In addition, most of the tension symptoms have been markedly reduced, the patient having a sense of well-being, a diminution in the amount of palpitation and headaches, and a lessening of the previously frequent dizzy spells. It is felt that this is primarily a relief of the tension syndrome rather than any therapeutic result as far as the hypertension itself is concerned.

Chlorpromazine has been used in the treatment of 8 cases of coronary occlusion and myocardial infarction in association with either Demerol or morphine. Although morphine has been the prime favorite in the relief of the apprehension of coronary occlusion, it has been found that with moderate doses of Demerol and rather large doses of chlorpromazine a similar apprehension-relieving combination can be found that seems to produce a very satisfactory relief of the discomfort but that does not produce the degree of respiratory depression so frequently seen in patients with coronary occlusion who have been sedated with large doses of morphine. In the use

of chlorpromazine in this condition, the hypotensive effects of the drug must be kept in mind, and close observation of the patient is mandatory.

Chlorpromazine has been used with very satisfactory results in the treatment of approximately 10 patients with recurrent angina pectoris. Prior to the advent of chlorpromazine, the treatment of angina pectoris resolved itself into the administration of xanthine derivatives and coronary vasodilators, of which Peritrate has seemed to be one of the most effective. However, in the past year these patients have been treated with a combination of Peritrate and chlorpromazine, which appears to be much more effective than the use of Peritrate alone. Whether this effectiveness is by virtue of relief of the anxiety and worries that accompany angina pectoris is unknown. However, it has been noted that in several patients in whom angina continued on the administration of adequate doses of Peritrate, the subsequent administration of chlorpromazine seemed to lessen to a moderate extent the number and severity of the attacks of angina pectoris.

Chlorpromazine has been used also in the irritable colon syndrome accompanied by constipation with intermittent diarrhea, mucoid stools, flatus, and abdominal cramps in which no evidence of organic disease could be noted. In such cases there has been a remarkable lessening of the tendency to diarrhea, and the patient has complained of much less abdominal cramping and has appeared to tolerate the drug extremely well. In several cases in which diarrhea was a troublesome complaint, the administration of chlorpromazine has resulted in a mild constipation that has been rather pleasing to the patient.

Many articles have appeared recently regarding the use of chlorpromazine in the treatment of asthma and status asthmaticus. I have had occasion to use the drug in approximately five episodes of status asthmaticus occurring in 4 patients. Chlorpromazine has been used after aminophylline, adrenalin, iodides, rest, antibiotics, and tracheal suction have not resulted in a satisfactory response. After the administration of intramuscular chlorpromazine, the patients appeared to have a rather moderate reduction in the respiratory rate associated with a marked diminution in the amount of wheezing and a marked tranquilizing effect. Most patients went to sleep shortly after administration of chlorpromazine, and during sleep no depression of respiration was noted. Bronchial spasm was gradually relieved, and there was moderate diminution in the tachycardia that these patients had experienced during their episodes of severe asthma. In almost all cases, after administration of chlorpromazine there was a slight transient drop in blood pressure; however, this has not been found to be serious and the blood pressure has usually reverted to normal within one to two hours. It is therefore suggested that in any episode of status asthmaticus, when routine therapy appears to be ineffective, the administration of chlorpromazine should be tried. In 1 patient, where hospitalization was necessary because of repeated episodes of severe asthmatic attacks that could not be controlled at home, the oral administration of chlorpromazine on a regular basis has diminished the frequency and severity to such an extent that, where previously he had been repeatedly hospitalized for treatment, he has now been undergoing treatment at home for three and one-half months, the longest period in three years that he has been out of the hospital.

Chlorpromazine has been used in the treatment of 3 cases of generalized and localized neurodermatitis in which severe itching was the prime complaint. In 1 patient in whom generalized pruritus had existed for approximately six months and which was refractory to all other forms of treatment, chlorpromazine produced a marked lessening of the pruritus, and the patient was able to obtain a good night's sleep for the first time in approximately three months. There appears to be no definite effect on the disease itself, for as soon as the administration of chlorpromazine was discontinued, the pruritus recurred with its former intensity. In such cases it is felt that a possible strong emotional factor may be responsible for the itching. In several cases of pruritus ani and pruritus vulvae in which local therapy had been only moderately effective, the administration of chlorpromazine, in conjunction with local therapy, appeared to alleviate the symptoms almost entirely. It is felt, therefore, that the administration of chlorpromazine in cases of chronic resistant neurodermatitis or itching in which insomnia, restlessness, and agitation are accompanying symptoms, some degree of relief may be obtained over and above that which could be obtained with local therapy alone.

PEDIATRICS

Chlorpromazine has been used in the treatment of 5 children who manifested hyperkinetic, aggressive, hostile behavior, and in all children a satisfactory result was obtained. However, in these children, rather large doses of the drug were essential for initial therapy, after which the dosage was reduced for maintenance therapy. There was a marked regression of the hostility and aggressiveness; the children became much calmer with a fair degree of relief of hostility.

In children, the most frequent use of chlorpromazine has been to control the nausea and vomiting so frequently seen in acute gastroenteritis in infants and young children. In such conditions the administration of oral chlorpromazine, in a sirup preparation, has been followed by a prompt remission of the vomiting and nausea in approximately 85 to 90 per cent of cases. In cases resistant to chlorpromazine therapy, where vomiting persisted in spite of repeated administrations of the drug orally, parenteral administration has been found to be highly effective in subduing the nausea so that oral administration of the drug may be started. In addition to its antiemetic effect, the tranquilizing effects of chlorpromazine have been extremely beneficial, tending to subdue much of the restlessness and fussiness of infants with gastroenteritis and vomiting. Chlorpromazine has also been used in the treatment of the pain and restlessness associated with otitis media, severe pharyngitis, respiratory infections, and laryngo-tracheo-bronchitis in children. For the past six to seven months it has been used routinely in preoperative and postoperative treatment of children subjected to minor or major surgical procedures. There has been a marked lessening in the tendency to vomit after ether anesthesia, and the children seem to emerge from the anesthetic much more smoothly. In many instances, the administration of chlorpromazine with barbiturates or aspirin has been sufficient to relieve postoperative pain so that narcotics are not required.

I have used chlorpromazine in the treatment of 18 cases of dysmenorrhea and tension

states occurring at the menarche with moderately good results. It has been effective in relieving much of the tension associated with the initiation of the menstrual cycle and in relieving the cramps of dysmenorrhea in younger women. In such instances it is advisable to administer chlorpromazine for approximately four or five days before the onset of the menstrual period.

OBSTETRICS

Chlorpromazine has been used during labor in approximately 110 obstetric cases in the past 14 months and has been highly effective in relieving the anxiety and apprehension during labor and delivery. There has been a marked diminution in the amount of nausea and vomiting in the patient in labor. Vomiting occurring prior to the administration of anesthesia and during anesthesia has been repeatedly incurred as one of the major causes of maternal morbidity and mortality. Serious illness and death from aspiration are still factors in the mortality of the obstetric patient. Due to the fact that the onset of labor is unpredictable, most women admitted to the hospital in active labor have recently ingested food. Although preanesthetic lavage of the stomach would be a desirable portion of the conduct of labor, it is so unpleasant that it is seldom resorted to. Therefore the administration of chlorpromazine during active labor appears to serve a satisfactory function in that it reduces the tendency to vomit both during labor and during anesthesia and subsequent delivery. In addition, it has been noted in approximately 6 cases that after the initial dose of chlorpromazine, which in my practice is administered at the time of admission to the obstetric ward, labor pain will occasionally cease entirely; and this has occurred with such a degree of regularity that in several instances it has automatically pointed to false labor without the need to watch the patient for 8 to 10 hours. We have concluded, therefore, that if labor ceases following administration of a single oral dose of chlorpromazine, it is false labor, and the patient is discharged.

In its use in approximately 110 parturients during labor and delivery, a satisfactory degree of analgesia has been obtained in almost all cases. The patients continue to have their labor pains regularly; however, the adequately sedated patient is almost somnolent between pains but is easily aroused for further medication or preparation and seems to assume almost a detached attitude toward her hospital environment and to labor. Rather than being apprehensive and anxious, the patient becomes almost placid in her outlook toward her future delivery. Because of the potentiating effect of chlorpromazine with analgesics and sedatives, I have used only 50 mg. doses of Demerol in addition to the intramuscular chlorpromazine as prepartum sedation. This has apparently been enough to keep the mother very calmly sedated; however, it has exerted little or no effect on the respiration of the newborn infant. In 110 consecutive deliveries there has been only 1 fetal death, which occurred within 24 hours after birth in a female infant born with multiple congenital abnormalities, among which was a congenital diaphragmatic hernia on the left with the entire stomach and spleen in the left chest and congenital heart disease. This baby breathed soon after birth; however, she remained cyanotic in spite of oxygen administration

and incubation and died 23 hours after delivery. In all other instances, no resuscitation was found necessary.

Occasionally, when multiple doses of chlorpromazine have been administered to a woman during a prolonged labor, a soporific effect on the baby has been noted in that the baby is moderately sleepy following delivery. However, respiration has been, in these instances, spontaneous and quick, but when the baby is placed in the incubator, he immediately falls asleep. Observation of the sleeping baby has revealed normal respiratory rate and excursions with no evidence of subsequent hypoxemia.

Less anesthetic agent has been required for these patients delivered under chlorpromazine-Demerol sedation, and in some instances the patient has delivered without any inhalation anesthesia and only local infiltration of the perineum for episiotomy and subsequent repair. Nausea and vomiting during delivery have been substantially reduced; no cases of postpartum pneumonia due to aspiration have been noted.

Insofar as the duration of labor is concerned, although it is difficult to note whether chlorpromazine has a tendency to affect the duration of labor, it would appear that most labors have been unaffected by administration of the drug. However, no control series has been run and therefore no conclusions can be drawn.

In numerous instances chlorpromazine has been used during the postpartum course of the patient; one of my pet uses has been in the treatment of the anxiety of primiparas in nursing newborn babies. It has been noted that those kept on adequate doses of chlorpromazine appear to be much calmer in caring for their babies, much more pleasant, and less apprehensive and that because of the tranquilizing effect of the medication, the milk supply has been slightly better. Many of the patients have been discharged from the hospital and maintained on chlorpromazine in adequate doses at home for approximately two to four weeks until the milk supply has been regulated. In such instances it has been found that the mother is much less apprehensive over nursing her baby and she is much calmer in her attitude toward her newborn child; this has significantly diminished the number of phone calls that the busy doctor gets from primiparas who are excited over their new arrival. Occasionally babies who are nursing will exhibit a placidity that has caused me to wonder whether chlorpromazine may be transmitted via mother's milk. No serious ill effects have been noted, and in only 1 instance was the drug discontinued because of this apparently soporific effect.

Insofar as the use of chlorpromazine in the nausea and vomiting of pregnancy is concerned, my results have been somewhat less spectacular than those reported in the literature. It was tried in approximately 40 consecutive patients who complained of moderate to severe nausea and vomiting and was effective in approximately one half of this group. It has been noted that the more severe the nausea, the greater the likelihood that chlorpromazine will be effective in its treatment. In mild cases of nausea with only occasional vomiting, the results are generally not as good. However, in the occasional instance of hyperemesis gravidarum, in which severe vomiting, weight loss, dehydration, and alkalosis are apparent, hospitalization and the parenteral administration of chlorpromazine along with intravenous fluids have been found to be extremely effective in controlling the vomiting. In such instances

the patient is maintained in the hospital for approximately one to two weeks, initially receiving parenteral chlorpromazine and subsequently changing to oral administration when nausea and vomiting are subdued. In this manner the drug has been found to be extremely effective and in 1 instance was almost miraculous in relieving the vomiting of hyperemesis gravidarum.

SURGERY

Chlorpromazine has been used in the preoperative and postoperative management of approximately 200 major and minor surgical patients. Approximately 110 of these have been major surgical cases undergoing abdominal and orthopedic surgery, and approximately 90 have undergone minor surgical procedures that include the local excision of lesions, both benign and malignant, cystoscopy, proctoscopy, rectal biopsy, fulguration, and urethral dilatation. Its use in the preoperative management of patients has resulted in a marked lessening of anxiety of the patient toward the coming surgery, a greater ease of induction of the patient under anesthesia, and maintenance under anesthesia with far less anesthetic agent to maintain a given level of anesthesia. In addition, the freedom from respiratory depression, which is so frequently seen in a heavily premedicated surgical patient, has been gratifying. The relative absence of respiratory depression in these patients receiving 25 to 50 mg. of chlorpromazine preoperatively in association with atropine, as compared to those receiving full doses of Demerol and morphine and atropine, is quite remarkable.

In its use preoperatively in children who are given ether anesthesia in our institution, there has been less reluctance to accept the anesthesia mask and less excitation in induction than were previously noted. However, the ease of induction becomes deceptive in some cases to those unfamiliar with chlorpromazine premedication, and it is not unusual to see a patient who is thought to be adequately asleep suddenly begin to stir or hold his breath when the operative procedure is begun. In children receiving ether anesthesia the usual premedication dose is approximately 0.3 to 0.35 mg./lb. given with a dosage of atropine calculated on the basis of body weight. In some severely agitated or belligerent children, up to 0.5 to 0.6 mg./lb. has been given preoperatively with no significant adverse reaction.

In adults, significantly smaller amounts of Pentothal and curare have been required for maintaining anesthesia, without the respiratory difficulties so frequently seen in heavily premedicated individuals. Preoperatively, in major surgery, either 25 or 50 mg. of chlorpromazine is given intramuscularly with atropine approximately one to one and one-half hours before surgery. In these patients less apprehension is noted in inducing anesthesia. In some instances where minor procedures are contemplated, the dosage of chlorpromazine may be substantially less. In routine cystoscopy and retrograde pyelography in women, 50 mg. of Demerol has been given with 50 mg. of chlorpromazine, and this has constituted the entire anesthesia for the procedure, no local anesthesia being required.

The most alarming side effect of chlorpromazine encountered in the postoperative period to date has been a moderate to severe hypotension, which has been noted postoperatively in approximately 25 to 30 per cent of the patients premedicated with

large doses of the drug. The blood pressure may show a significant drop, usually noted on moving the patient from the operating room back to the recovery room or to the bed. In some instances the blood pressure has fallen to 60 to 80 systolic over 40 to 60 diastolic, alarming the attending physician and nurses. During the first few experiences with this hypotensive phenomenon, vasopressers were used to attempt to raise the blood pressure; however, none of the drugs used (Vasoxyl, ephedrine, Desoxyn) was found to raise the blood pressure consistently in the hypotension encountered. It was soon noted that, given adequate fluid replacement, the blood pressure consistently rose within an hour or two to adequate levels if the patient was maintained in Trendelenburg position. In some instances, it is difficult to differentiate between the hypotensive effects of chlorpromazine and the hypotension of true shock. In our experience the hypotension induced by chlorpromazine has seldom lasted more than 30 to 60 minutes. The typical clinical pattern of shock is absent, the patient being warm, dry, and asleep, with slow, regular respiratory pattern. There is no evidence of sweating, the pulse rate is usually maintained at a normal or only slightly increased level, nail beds are pink, and the urinary output does not appear to be influenced at all.

Conversely, the typical pattern of true shock reveals the patient to be of cyanotic hue, with labored respiration, cold, clammy skin, collapsed veins, a weak, thready, rapid pulse, and a continually falling blood pressure. This picture has never been encountered in chlorpromazine-induced hypotension.

Postoperatively chlorpromazine has been used in conjunction with Demerol for the treatment of postoperative pain and has been found to be adequate for the relief of almost all types of pain. Morphine has not been found necessary. With the use of Demerol and chlorpromazine there has been a lessened tendency toward respiratory depression and the patients have exhibited much less anxiety over their pain and appear to be much more comfortable. The incidence of respiratory complications following upper abdominal surgery seems to be markedly lessened, and only a single case of postoperative atelectasis has been noted in approximately 110 surgical procedures.

TERMINAL MALIGNANCIES AND UREMIA

Chlorpromazine has been used in the treatment of approximately 4 patients with terminal malignancy with excellent results. Previously these patients had been maintained on large doses of opiates. Initially the dosage of opiates was reduced and the patients were given chlorpromazine in addition to the previously administered opiates. In 2 patients the necessity for opiates gradually diminished until, finally, both were being maintained on chlorpromazine alone in a very satisfactory manner. Both patients were treated at home without the necessity of intramuscular or oral administration of large doses of opiates, which are so frequently required in terminal malignancy patients.

Chlorpromazine has also been used in the treatment of 2 cases of nausea and vomiting due to uremia. In 1 patient uremia was the result of an advanced Kimmelsteil-Wilson syndrome and diabetes, and in the second it was due to advanced terminal

glomerulonephritis. Initially the patients were given chlorpromazine by parenteral administration; however, when vomiting ceased and the patients appeared to tolerate oral medication satisfactorily, chlorpromazine was begun orally and continued satisfactorily up to the time of death. Its use in such cases appears to be remarkable in alleviating the severe nausea and vomiting and the depression and attitude of defeatism so frequently seen in terminal patients. In addition, the families have noted that the patients are much less irritable, create much less tension in the household, and appear to be much more resigned to the outcome, with less anxiety.

DOSAGE

Insofar as the dosage of chlorpromazine is concerned, this must be adequately decided for each individual patient on the basis of therapeutic trial. No one method of treatment or no one dosage will be required for all patients. In the average patient, the administration of 10 mg. three or four times daily is begun and the patient is observed closely over a period of three to four days to see the initial response. In approximately 10 per cent of the patients, even this dose will be found to be more than can be tolerated without side effects, and a lesser dosage will finally be decided upon. However, in the great majority of patients, the dose will gradually have to be increased by 10 to 30 mg./day, depending on the tolerance of the patient, until a satisfactory maintenance dose is reached that is slightly short of the amount that produces drowsiness or lethargy in the patient. The average dose of chlorpromazine is approximately 75 to 100 mg./day; however, in some instances a dosage of 400 to 500 mg./day will be found necessary.

In the treatment of severely agitated cases, larger doses are practically always necessary and in such cases, the initial parenteral therapy in the hospital is strongly advised. Upon attaining a satisfactory level, a gradual reduction of dosage may be begun until a satisfactory maintenance level is reached, and this may be continued for indefinite periods although the patient should be watched closely during the first few weeks of administration.

In the treatment of severely agitated patients, acute alcoholics, and persons with acute psychoses, hospitalization is recommended so that parenteral administration may be started, for it is difficult to get a severely agitated patient to take adequate amounts of medication by mouth. In such instances the initial dose should be 25 mg. muscularly given every four hours. If such dosage does not appear to be adequate, the dose may be raised by 50 mg. to 100 mg./day until a satisfactory dosage level is obtained. The largest dose that I have had occasion to use in my particular practice has been 1000 mg./day given to a severely agitated paranoid schizophrenic. The dosage in this instance was begun at 50 mg. four times daily and raised by 50 mg. increments at each dose until a total of 250 mg. was given five times daily intramuscularly to achieve a satisfactory degree of sedation.

SIDE EFFECTS

It is my belief that side effects attributed to chlorpromazine have been highly overemphasized in the literature. Many articles have been devoted to the incidence of

chlorpromazine-induced jaundice, and several papers have appeared on deaths due to the administration of the drug. In my experience there have been no deaths and only 2 cases of jaundice, both of which will be described below.

The most notable side effect of chlorpromazine administration is the drowsiness and sleepiness that occur in approximately 10 to 15 per cent of the patients receiving an adequate dose. In such instances, if the dose of chlorpromazine appears to be adequate to subdue the tension and anxiety symptoms that one is attempting to treat, then satisfactory response may be obtained by the administration of small amounts of dexedrine to relieve the sleepiness.

A second reaction that is occasionally noted is a mild febrile reaction which will usually occur during the first three or four days of therapy; however, it is unattended by any general systemic response and will usually clear spontaneously in just a few days. Occasional patients will notice a rather marked dryness of the mouth, and in several instances, patients have complained of a metallic taste in the mouth occurring during the administration of chlorpromazine. However, these side effects are minimal, and it has been necessary to discontinue administration of the drug in only 1 patient because of extreme dryness in the mouth and irritation.

Urticarial reactions have been described in the literature and have been noted in 2 of the 1600 patients who have received chlorpromazine. One was a 17 year old white girl who was receiving the drug primarily for paroxysmal palpitation, for which no organic disease could be found, and for moderate tension and nervousness. She had always been described as a "nervous child," and the palpitation had begun approximately six months before the institution of therapy. This patient developed a brief urticarial reaction over the face associated with mild swelling and itching which subsided within 24 hours after discontinuance of the chlorpromazine. The second patient was a 27 year old man who was under treatment because of a chronic anxiety state marked by somatic symptoms consisting of palpitation, epigastric distress, paroxysmal sweating, and frequent tension headaches. No organic disease could be found on physical examination or laboratory studies. Roentgenograms were entirely negative, and the electrocardiogram was within normal limits. The patient was placed on chlorpromazine, beginning with an initial dose of 25 mg. three times daily. On the fourth day of therapy the patient developed urticarial lesions over the face, chest, back, and abdomen, and chlorpromazine therapy was discontinued. The urticaria subsided within 24 hours with only local therapy and has not recurred.

In approximately 5 per cent of patients receiving chlorpromazine, palpitation may become a troublesome complaint, and in such cases discontinuance of medication becomes necessary. In some instances reassurance of the patient that his heart symptoms are due to the therapy has been sufficient to relieve the distress. However, in many instances an alternate form of therapy becomes necessary.

Insofar as jaundice is concerned, 2 patients of the 1600 treated have developed icterus. In case 1 the possibility that icterus was due to chlorpromazine was quite real. In case 2 it was questionable that the drug induced the icterus, and this was never definitely proved.

Case 1. B. W., a 38 year old man with a history of duodenal ulcer dating back to

1947, developed recurrence of symptoms in August 1955, which responded well to banthine, antacids, Sippy diet, and bedrest. He got along quite well until December 1955, when he complained of nervousness, impatience, and occasional alcoholic bouts. The patient was placed on chlorpromazine, 25 mg. three times a day, and felt quite well for four days. On the fifth day, the patient had epigastric tenderness, dark urine, and a low grade temperature. The urine was 2 plus for bile. Chlorpromazine was discontinued and the patient was followed daily in the office. The icterus subsided in five days uneventfully; it has not recurred in the past two months.

Case 2. N. A., an 80 year old woman, had a 30 year history of gall-bladder disease and a nine month history of a peptic ulcer. She had had repeated episodes of gall-bladder colic, and roentgenograms in the past revealed a nonfunctioning gall bladder. The duodenal ulcer had been found in April 1955 and had responded to therapy with no further symptoms.

On the most recent occasion, the patient was seen at home on Nov. 26, 1955 with a two week history of epigastric distress and colicky right upper quadrant pains, dyspepsia, anorexia, nausea, and occasional vomiting. She also developed severe, sharp right upper quadrant pains which did not subside. The patient was seen at home and given Demerol, 50 mg., and chlorpromazine, 25 mg., by injection. Because she refused hospitalization, she was given 50 mg. Demerol tablets and 25 mg. chlorpromazine tablets to take orally for pain. She was not heard from for three days, at which time her daughter called to tell me that the patient was jaundiced. Over this three day period, the patient had taken a total of 275 mg. of chlorpromazine.

When seen at home on November 29, she was moderately icteric with yellow sclerae, dark urine, acholic stools, and marked pruritus. She was immediately hospitalized for therapy.

Intravenous cholangiograms done on November 30 and again on December 5 revealed no visualization of the biliary tree. The laboratory studies on admission were as follows: hemoglobin, 12.0 Gm. white blood count, 9,050 with a normal differential; urinalysis, 5 to 8 white blood cells/high power field and 2 plus bile; sedimentation rate (Westergren), 91 mm. in one hour; icterus index, 37.2 units; van den Bergh reaction, one minute, 4 mg. per cent—total, 6.1 mg. per cent; thymol turbidity, 3 units; cerebrospinal fluid, negative at 24 hours, trace at 48 hours; alkaline phosphatase, 15.8 King-Armstrong units; urine urobilinogen, 0.3 Ehrlich units in two hours; prothrombin time, 100 per cent.

The patient was hospitalized for one week, during which time the icterus index and van den Bergh reaction revealed no essential change. However, the alkaline phosphatase increased to 27.4 units on December 6.

On December 6, surgical consultation was obtained and the opinion was that the patient had a common bile duct stone; surgical exploration was advised. The patient, however, refused surgery and left the hospital and went home. She has not been heard from since that time and therefore the state and cause of the icterus cannot be definitely determined.

SUMMARY

An attempt has been made to cover briefly some of the uses of chlorpromazine in

general practice. Many points have only been touched upon. It is apparent that chlorpromazine is a valuable tool in the armamentarium, not only of the psychiatrist, neurologist, obstetrician, or anesthesiologist, but also of the general practitioner. It is a drug that, when used discriminately and with careful observation, can be effective in treating many of the "neurotic" patients who are so frequent to everyday practice. It is also effective in alleviating the anxiety associated with organic disease, obstetric delivery and labor, postpartum anxiety, and surgery. Chlorpromazine can be regarded as one of the major drugs in the treatment of the mentally ill and in the treatment of mental and emotional reaction to organic illness. Because of its effectiveness, its simplicity of administration, its availability, and especially its freedom from serious side effects, it is felt that this will *not* be one of the "miracle drugs" to fall early by the wayside, as so many drugs of the past have done.

Egas Moniz Dies

The Editors of the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS regret to report the death on Dec. 13, 1955, of Professor Antonio Caetano de Abreau Freire Egas Moniz.

Professor Moniz, a member of the International Editorial Board of the *Journal of Clinical and Experimental Psychopathology*, was known the world over for his work on cerebral angiography, which he initiated in 1927, and for his pioneer surgical procedure of prefrontal lobotomy, which he first performed in 1935. He conceived the idea for this revolutionary treatment of psychoneuroses while attending the International Neurological Congress in London, and in 1949, he received the Nobel Prize for this work.

Professor Moniz was born on Nov. 29, 1874, in Avanca, Portugal, and was educated at the universities of Coimbra, Bordeaux, and Paris. Until 1911 he was professor of neurology at the University of Coimbra, and afterwards he held the chair of Professor of Neurology at the Faculty of Medicine in Lisbon. Other posts included that of director of the Institute of Neurology for Scientific Investigation and physician at the Hospital of Santa Marta in Lisbon.

His political and diplomatic career included service as a deputy in the Portuguese Liberal Parliament, Minister to Madrid in 1918, President of the Portuguese Delegation to the La Paz Conference in 1918, and Minister for Foreign Affairs from 1918 to 1919. In 1951, he declined the offer of the Republican and Socialist parties to stand as a candidate in Portugal's presidential election.

Among Professor Moniz's many academic affiliations were membership in the Lisbon Academy of Sciences, the Paris Academy of Medicine, the Brazilian Academy of Letters, the Brazilian Academy of Medicine, the Madrid Academy of Medicine, and Honorary Member of the Royal Academy of Medicine. He was awarded the Grand Cross of Isabella the Catholic of Spain, the Grand Cross of Public Instruction (Portugal), the Grand Cross of Santiago de Espada, and was made a Commander of the Legion of Honor.

Use of the Tranquilizing Properties of Reserpine

A Review

J. Campbell Howard, Jr., M.D., and Frank J. Vinci, M.D.

SUMMIT, N. J.

PHARMACOLOGY

The essential pharmacologic effects of reserpine (Serpasil*), isolated and identified by the Ciba team of Mueller, Schlittler, and Bein, consist of two main properties: (a) the ability to decrease sympathetic nervous system activity and (b) the ability to tranquilize.[1]

A characteristic of emotional turmoil is an overplay of the sympathetic nervous system, often causing tachycardia, pallor, clamminess, increase in blood pressure, and other similar symptoms. The same mechanism by which reserpine reduces blood pressure can alleviate these effects of hyperexcitement. With the decrease in adrenergic outflow, there may result a parasympathetic predominance that can account for some of the side effects of the drug such as cardiac slowing and increased bowel activity. Actually, some of these so-called side effects together with the sedative properties can be put to good use. These will be considered later.

The tranquilizing action of reserpine, allaying irritability and irritation, unlike that of the barbiturates or other hypnotics is not achieved by cortical depression. As a matter of fact, according to Rinaldi and Himwich,[2] "reserpine produces an alert electroencephalographic pattern" whereas the "barbiturates induce a pattern of sleep." Thus, to explain this action, we must look further. "The chief central mechanisms through which emotional behavior is mediated are known to be located in the hypothalamus."[3] From various studies it appears that the hypothalamus is involved. Schneider et al[4] have shown that the sham rage of a decerebrate cat can be controlled by reserpine.

CLINICAL USES

Being accustomed to the general rule of specific medications for specific conditions, the broad indications for reserpine may make it sound somewhat like the famous old "patent remedy." However, the wide gamut of uses is not so far fetched as it may appear on first impression. There are very few illnesses that do not require emotional adjustment, and therefore, as will be shown, its wide prescription is logical.

Neuropsychiatric Application. TRUE PSYCHOSES. In view of the vast amount of studies reported in the literature concerning the role of reserpine in the treatment of disturbed psychotics, mental deficiency, and behavior problems, the subject is only listed and will not be considered in detail.[5–8]

PSYCHONEUROSIS. In this group of disorders, such as anxiety reactions, hysteria,

* The trade name of Ciba Pharmaceutical Products, Inc. for reserpine is Serpasil.

or phobic reactions, the patient overreacts to various stimuli. Reserpine tones the reactions down, insulating the patient from his environment. This can be illustrated by the remarks of one of Wilkins' female patients: " 'I am not less ambitious, I'm not less aggressive, I'm not less effective. I just don't seem to *have* to do the things I used to. Before, I felt I had no control over myself. I *had* to do things. Now I don't care, I don't even notice things. Dust doesn't annoy me. Before, I knew it wasn't important, but I had to clean it up. Now I let it go for two weeks, and it doesn't bother me.' "[9] A further practical use in this connection is in the patient with globus hystericus.[10]

Clinical evidence indicates that reserpine should not be used in depression or depressive states except in those patients who are perhaps on the way out of a depression or withdrawal state, reaching the point where they are making some restitutive change. At this time their anxiety can be controlled so that they can devote more of their emotional drive to overcoming conflicts.

Dosage: The psychotic group requires large doses, usually starting with 5 mg. parenterally and increasing up to 10 mg. or more if necessary. Generally, 3 to 5 mg. is given at the same time by mouth, and after one to three weeks, oral medication alone (5 to 15 mg.) may be enough. For the neurotic, 0.1 to 1 mg./day will generally be sufficient.

These dosage recommendations do not constitute a hard and fast rule. The dose should be individualized according to the patient's response. Once maximum therapeutic effects are reached, as a general rule, the amount of medication should be reduced to the minimum that will maintain the desired effects.

Psychosomatic Medicine. Under this heading will be considered the conditions in which emotional tension may cause or aggravate physical symptoms, the control of which will usually lead to greater or more rapid improvement or better adjustment to the disability.

Cardiovascular System Disorders. Hypertension: In the treatment of hypertension, besides its ability to reduce blood pressure by its effect on the sympathetic governing center, the sedative properties afford a means of helping the patient to worry less over his diagnosis, his business, or other problems that tend to aggravate or perpetuate hypertension.

Post–Coronary Occlusion: Anxiety, depression, and tachycardia are all frequent findings after a myocardial infarction. The use of reserpine causes the patient to relax, helping him to accept the disability, and also reduces the heart rate to a more normal pace.[11] Angina pectoris might also be included under this category. Slowing of the cardiac rate allows more time for coronary filling. Decreasing the anxiety may also help lessen the attacks.

Rhythmic Disturbances: A common side effect of reserpine is cardiac slowing, due to a depression of the sympathetic nervous system and a resultant parasympathetic predominance exerted over the vagus pathways. Attacks of paroxysmal auricular tachycardia so frequently seen in high-strung persons can sometimes be prevented by the drug, but it has no place in the treatment of an acute attack.[12] The anxieties caused by premature auricular and ventricular contractions may be lessened by the patient being made less conscious of them or by a reduction in their occurrence.[11]

Neurocirculatory Asthenia: The so-called soldier's heart or man with the soiled shirt (from putting his hand over his heart) can be helped by both actions of reserpine.[11]

Dosage: In these cardiovascular disorders, 0.1 to 1 mg./day has usually been sufficient. Once full benefits have been achieved, the dosage should be reduced to a lower maintenance level. Frequently 0.1 mg./day is enough even for the hypertensive.

Functional Gastrointestinal Disorders. Functional gastrointestinal upsets, mucous and ulcerative colitis, are all closely tied to emotional disturbances and in many instances are caused by them. Reserpine's tranquilizing action has been found to be very helpful in preventing or decreasing the frequency and severity of these attacks.[13, 14] In spite of the fact that reserpine, due to vagal predominance, will increase gastric volume, acidity, and intestinal motility,[15, 16] apparently the sedative effect can more than offset these side effects in some instances.[14] In other words, in many of these patients the psychic factors must play a major role. Antacid and anticholinergic medication such as oxyphenomium bromide (Antrenyl*) should be given together with reserpine, particularly during its use in functional upper gastrointestinal lesions.[14]

Dermatologic Conditions. There is no question that psychogenic factors greatly influence the progress of many skin diseases as well as causing them. Rein and Goodman, Genest et al, and others have reported reserpine to be helpful in a variety of disorders such as chronic eczema, lichen planus, hyperhidrosis, neurodermatitis, urticaria, and some cases of psoriasis.[17–19] It should not be considered specific therapy but an adjuvant, although where nervous factors are the prime cause, perhaps reserpine alone may clear up the lesions. Because it may take several weeks for the full effects of the drug to be obtained, immediate results cannot be expected. However, even after three or four days of treatment, pruritis may be dramatically relieved.[20] Why it should be so helpful when itching is present is difficult to explain.

Obstetrics and Gynecology. Reserpine may be helpful in all of the following conditions: premenstrual tension, dysmenorrhea, menopausal syndrome, frigidity, and nymphomania.[21, 22] For premenstrual tension and dysmenorrhea, reserpine should be taken for 10 days before the expected menses; for menopausal symptoms, continuously. Whatever the cause, the theories being numerous, there is little question about there being a state of tension in the premenstrual syndrome. In the menopause, there are anxieties and fears and in many patients a hyperreactive vascular system, all of which can be aided by reserpine.

Even though frigidity is the direct opposite of nymphomania, according to Greenblatt,[22] reserpine is effective in either case. This can be explained in the following manner. The sexual response of the human female is tempered and influenced by many factors: psychogenic, anatomic, physiologic, and state of health. Whereas most men are in a constant state of frenzy, women, for the most part, demonstrate either a passive acceptance or a passive resistance. Few of them have that positive drive known as "libido." The frigid female does not enjoy marital relations because

* The trade name of Ciba Pharmaceutical Products, Inc. for oxyphenomium bromide is Antrenyl.

of latent or patent hostility for the "stronger sex" and refusal to accept a subordinate position. Her frigidity is, in fact, a form of pugnaciousness. With the administration of reserpine to 5 frigid women, libido per se as a positive force was not noticeably increased, but receptivity was so improved in 2 of them that they willingly accepted their mates. On the other hand, in 2 women with such nymphomaniacal tendencies as to prove disturbing to their husbands and to themselves, the sedating action of reserpine proved of decided advantage in lessening the constant urge. Reduction in the tension states causing these conditions brought the patients' responses to a more acceptable level.

Weight Gaining. There is a general tendency for some patients on reserpine to gain weight. This actually can be put to good use. Many people without specific disease, characterized by Shakespeare's "lean and hungry look," as well as those with illness such as tuberculosis are emotionally high strung to a degree that it either affects their eating habits or makes them burn off what they eat. Calming the individual and reducing the expenditure of nervous energy allows him to relax, take time to eat, eat more, and not burn up calories so fast. For the tuberculous patient, in addition to helping him gain weight, reserpine can help him adjust to his disability.

Although no studies have been carried out, the sedative properties might help the overweight bulimic individual, who eats and eats because of emotional problems, lose weight by lessening his tensions and therefore his dependence on oral gratification.

Headaches. According to Barrett and Hansel,[23] reserpine is effective in vascular types of headaches regardless of the basic mechanism involved. It is especially useful in the histaminic type, which is the most common of the vascular headaches. Friedman[24] also reported that it has value in tension headache, particularly of the hypertensive variety, but has little effect on migraine. Of course, the use is prophylactic and the drug is not for acute cases.

Bronchial Asthma. Pharmacologically, a sympathetic stimulation, as with the administration of epinephrine, to relax the constricted bronchioles is the general rule in treating the acute asthmatic attack, not the use of a sympathetic depressant such as reserpine. However, all who have had anything to do with asthmatics are cognizant of the role that emotional disorders play in triggering an asthmatic attack. Segal and Attinger[25] reported that of 56 chronic bronchial asthmatics, 4 had less dyspnea and 22 were not as jittery or disturbed. Acute attacks were less severe and less prolonged and could be more easily relieved with standard measures.

Dosage: For all the above-listed conditions, a range of from 0.1 to 1.0 or 2.0 mg. of reserpine has been employed. Generally, once the full effects have been obtained, the dose can and should be reduced to a lower maintenance level. Because reserpine requires at least two to four days to begin to work, and up to four or more weeks to produce full effects, it makes no difference whether the total daily dose is given once a day or is divided—results are the same either way. The dosage for the remainder of the indications will be discussed under the specific use, as different amounts are required in these instances.

Pediatric Use. High-strung, tense children and those with behavior disorders

can be relieved by the tranquilizing action of reserpine. Since children tolerate the drug well, even fairly large doses (up to 5 mg./day or more) can be employed. The more disturbed the child, the larger should be the dose. Talbot[26] reported that 29 per cent of 32 infants, 6 weeks to 1 year old, who were hyperactive, irritable, and had bizarre sleeping patterns were helped. On doses of 0.1 to 0.3 mg./day, there was complete remission of irritable behavior in 19 cases.

Enuresis in 16 of 17 children responded without other medication or fluid restriction. The single failure was found to have a duplication of one ureter. The average dose was 0.75 mg./day.[27]

Geriatric Use. Both the so-called normal geriatric patient and the senile psychotic can be helped. In the former group, Ayd[28] reported that on reserpine the geriatric patient adjusted better to his situation, both at home and in nursing homes, and could remain there instead of entering a psychiatric institution. Sainz,[29] in a study of 750 ambulatory and hospitalized elderly psychotics, found considerable improvement in behavior and a lessening of quarrelsomeness, apprehension, and negativism. The dosage should be individualized depending on the severity of the symptoms and the response.

Alcoholism. The unsatisfactory management of the acute alcoholic, particularly of his excitement, tremors, and hallucinations, with hypnotics such as paraldehyde is well known. For adequate sedation, the patient must be knocked out and he may develop pneumonia and urinary infections, becomes a nursing problem, and may become addicted to the hypnotic. Neuer, Avol and Vogel, Greenfield, and others,[30–33] studying the tranquilizing properties of reserpine, found that such patients could be quickly brought under control, some within as few as nine hours and all within 48 hours. On an average, patients were symptom free in 24 hours. To obtain more rapid effects, one or two 2.5 to 5 mg. doses were given parenterally about three hours apart. A repeat parenteral dose was given the second and third day, if necessary; otherwise, 0.5 to 1 mg. of reserpine per day was given by mouth. Patients quieted down but were not forced to be bedridden as a result of heavy sedation. Greenfield[32] treated 28 patients with a milder variety on an outpatient ambulatory basis, starting them with a parenteral dose of 2.5 mg. Later in his work he found that the addition of 10 mg. of oxyphenomium bromide three times a day by mouth was helpful in settling intestinal upset associated with the alcoholism. The dosage should be individualized for each patient and the drug used cautiously in patients on Antabuse or with cardiovascular problems. The blood pressure reduction may be greater in the latter groups. Several investigators have alluded to the possibility of long term therapy with reserpine by mouth, helping to lessen the emotional problems that lead to drinking and thereby aiding in rehabilitation. This would have to be combined with an adequate medical and Alcoholics Anonymous program. West,[33] at the American Psychiatric Association Meeting in May 1955, reported success in 25, improvement in 7, and failure in 8 persons under such a program begun in January 1953, but to prove its value further, more extensive trials are needed.

Head Injuries. The use of opiates and hypnotics in acute head injuries or postcraniotomies is not advisable because of the masking of vital signs such as pupillary size and respiratory rate by these drugs. Lambros[27] and Steelman[34] have both re-

ported that when reserpine was used, vital signs were not masked and patients were not restless and could help themselves. Lambros[27] also found that abnormal neurologic signs and symptoms regressed more rapidly and headache was negligible. "Ten patients with acute closed type of head injuries were given Serpasil 1 to 2 cc. (2.5 to 5 mg.) every 2 to 3 hours intramuscularly. No patients who were in shock were treated with Serpasil."[24]

Convulsive Disorders. Lambros[27] and Barsa and Kline[25] found the tranquilizing effect of reserpine helpful, not so much as a preventative, but more in terms of sedation and of aiding the patient to adjust to the difficulty. From 0.5 to 1.5 mg. of reserpine was given.[27]

SIDE EFFECTS

Before giving any drug, one should have a knowledge of what it can do, how it works, and what side effects may occur. If it is recalled that reserpine decreases sympathetic nervous system tone, allowing parasympathetic predominance, many of the so-called side effects that are actually normal physiologic responses can be easily remembered, such as, nasal stuffiness, nausea, increased intestinal activity, cardiac slowing, and reduction in blood pressure (usually not below normal). Lethargy or tiredness can be explained on the basis of the tranquilizing action. Generally, most of these symptoms subside as therapy is continued. If they are bothersome, however, "side effects may be adequately controlled by reduction of dosage

TABLE 1

Side Effects and Their Management

Side effect	Management
Nasal stuffiness	Topical vasoconstrictors such as naphazoline*
	Antihistamines orally or topically such as tripelennamine†
	Methyl-phenidylacetate may also help
Bradycardia	Usually not sufficient to be troublesome; lower dosage
Hypotension	Usually not a problem—bed rest and, if severe, *l*-arterenol
Gastrointestinal complaints	
Nausea or vomiting	Anticholinergics such as oxyphenonium bromide and antacids
Diarrhea	Reduce dosage—usually subsides without treatment
Lassitude and drowsiness	Methyl-phenidylacetate, 5 to 10 mg. 3 times a day; reduce dosage
Depression—usually preceded by agitation, insomnia, also a history of depressive tendency	Stop medication and methyl-phenidylacetate may be given
Side effects seen during psychiatric use—high dosage	
Turbulence and agitation (Kline turbulent phase)	Glutethimide,‡ 0.5 to 1 Gm., may quiet patient (Barsa and Kline[25] feel this is an important phase of therapy); some reduce dosage
Parkinson-like syndrome	Reduce dosage
Convulsive episodes	In psychotic patients occasionally they may occur during early weeks of therapy; handle on individual basis

* The trade name of Ciba Pharmaceutical Products, Inc. for naphazoline is Privine.

† The trade name of Ciba Pharmaceutical Products, Inc. for tripelennamine is Pyribenzamine.

‡ The trade name of Ciba Pharmaceutical Products, Inc. for glutethimide is Doriden.

TABLE II

General Indications and Dose Range

Indications	Daily dosage range
1. True psychoses	2.5 to 5 mg. intramuscularly plus 1 mg. twice a day orally
2. Psychoneurosis	0.25 to 1 mg. orally
3. Cardiovascular disorders	
a. Hypertension	0.5 to 1 mg. orally
b. Post-coronary occlusion	0.1 to 1 mg. orally
c. Rhythm disturbances	0.1 to 1 mg. orally
d. Neurocirculatory asthenia	0.1 to 1 mg. orally
4. Functional gastrointestinal disorders	0.1 to 0.5 mg. orally plus oxyphenomium bromide, 10 mg. 4 times a day
5. Dermatologic conditions	0.25 to 0.5 mg. orally
6. Obstetrics and gynecology	
a. Premenstrual tension	0.25 to 1 mg. orally
b. Dysmenorrhea	0.25 to 1 mg. orally
c. Menopausal syndrome	0.25 to 1 mg. orally
d. Frigidity and nymphomania	0.25 to 1 mg. orally
7. Weight gaining	0.1 to 1 mg. orally
8. Headaches	0.25 to 1 mg. orally
9. Bronchial asthma	0.25 to 1 mg. orally plus antiasthmatic therapy
10. Pediatrics	
a. Hyperkinetic children	0.2 to 5 mg. orally
infants	0.1 to 0.3 mg. orally
b. Enuresis	0.25 to 1.5 mg. orally
11. Geriatrics	
a. Normal geriatrics	0.25 to 1 mg. orally
b. Senile psychoses	3 to 5 mg. orally
12. Alcoholism	
a. Acute phase	2.5 to 5 mg. parenterally repeated in 3 hours if necessary
b. Chronic phase	0.5 to 1 mg. orally. The addition of oxyphenomium bromide, 10 mg. 3 times a day, is helpful in settling intestinal upset associated with alcoholism
13. Head injuries	2.5 to 5 mg. intramuscularly every 3 hours
14. Convulsive disorders	0.5 to 1.5 mg. orally

or by the addition of other drugs: lethargy—Ritalin;* nasal stuffiness—antihistamines; jitters—lower dosage; nausea—Antrenyl."[36] The development of a Parkinson-like syndrome or of the agitated behavior that is described by Kline[37] as the turbulent phase of reserpine therapy is an effect that occurs on higher psychiatric dosage, such as 10 to 15 mg./day or more, when reserpine is given by the parenteral route and not when employed for the above conditions.

The most serious reaction that may occur is the onset of a depressive syndrome, as reported by Freis and others.[38–40] In patients whose level of activity is lowered at the start of therapy, or who have a history of a depressive tendency, the drug should

* The trade name of Ciba Pharmaceutical Products, Inc. for methyl-phenidylacetate, a new product, is Ritalin.

be used with caution, if at all. If one is to employ reserpine, low dosage should be used and an analeptic drug such as methyl-phenidylacetate hydrochloride may be given concomitantly. Ayd, Ferguson, and others have found that the latter counteracts the lethargy associated with reserpine therapy.[41–42]

In several cases of reserpine-induced depression, Ferguson[42] reported that "administration of phenidylate* to these patients appeared to overcome the depression and clear the drowsiness sufficiently to permit an awakening-to-reality and some physician-patient contact." Ayd[41] has not found this to be true. Further study will be necessary before the exact influence of Ritalin in reserpine-induced depression can be determined.

The development of insomnia, agitation (except in psychotics), or symptoms of mental depression, which are to be differentiated from lethargy or tiredness, calls for watchfulness on the part of the physician. The dose of reserpine should be reduced or discontinued. Some of the patients showing these signs have gone on to develop a depressive reaction.

SUMMARY

1. The essential pharmacologic actions of reserpine, namely, the tranquilizing effect and reduction of sympathetic reactivity and parasympathetic nervous system predominance, are reviewed.

2. The uses of the tranquilizing effect in hypertension, post–coronary occlusion, rhythmic disturbances, neurocirculatory asthenia, true psychoses, psychoneurosis, functional gastrointestinal disorders, dermatologic conditions, obstetrics and gynecology, weight gaining, headaches, bronchial asthma, pediatrics, geriatrics, alcoholism, and head injuries are discussed.

3. The dosage recommendations for the above conditions are given.

4. Side effects, their significance, and their management are reviewed.

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* Ritalin.

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The Use of Azacyclonol and Pipradrol in General Practice

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A number of new compounds have recently been developed for the treatment of nervous and mental diseases. Most of the original clinical research was conducted by neurologists and psychiatrists, but the practical applications of these drugs in the field of general practice are probably even greater. Two of the drugs most likely to be confused with one another are pipradrol (Meratran*) and azacyclonol (Frenquel†). These two compounds are isomers of each other. The structures are usually represented as shown in figures 1 and 2.

It appears that these two compounds both influence that portion of the brain concerned with the function of alerting.[1] Varying with the activity of the septal area or the reticulodiencephalic-activating system, the person may be very alert, moderately wide awake, drowsy, asleep, or psychotically out of contact with his surroundings. Therefore, the various diseases in which pipradrol or azacyclonol is indicated are, in general, psychosomatic disorders. However, the effect of these two compounds on the alerting system of the brain is different and, in some respects, somewhat the opposite.

Pipradrol stimulates the alerting mechanism of the brain, but it differs from the amphetamine group of compounds in that it is not a sympathomimetic amine and it has virtually no effect on the peripheral nervous or cardiovascular systems. In contrast to pipradrol, azacyclonol is neither a stimulant nor a depressant of the normally functioning alerting system. When the alerting system of the brain is functioning normally, it is difficult to demonstrate any pharmacologic effect of azacyclonol in human beings or experimental animals. But when this alerting system is behaving in an abnormal manner, as a result either of experimental conditions or of spontaneous disease, the action of azacyclonol appears to correct this abnormality. Accordingly, it is an anticonfusion drug, sometimes described as antihallucinatory or antidelusional.

PIPRADROL

The pharmacologic effects of pipradrol in experimental animals were described by Brown and Werner.[2] They found that it produces a measurable increase in coordinated and purposeful activity. This effect is grossly similar to that which can be produced by suitable doses of amphetamine. However, there are important differences. Of great significance is the absence of a period of depression following

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* The trade name of the Wm. S. Merrell Company for pipradrol, or α-(2-piperidyl) benzhydrol hydrochloride, is Meratran.

† The trade name of the Wm. S. Merrell Company for azacyclonol, or α-(4-piperidyl) benzhydrol hydrochloride, is Frenquel.

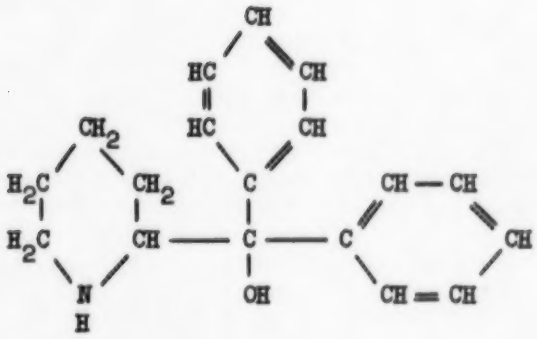

FIG. 1. Pipradrol (Meratran).

the period of pipradrol stimulation. This period of depression following amphetamine is believed to reflect in experimental animals something comparable to the letdown that occurs after a period of amphetamine stimulation in human beings. In addition to this absence of afterdepression, it was noted that pipradrol does not possess the sympathomimetic and pressor effects that are characteristic of amphetamine.

Fabing et al[3, 4] conducted exploratory studies with pipradrol in human beings, in the belief that a central stimulant that has properties demonstrated in experimental animals to be different from those of other stimulants should behave differently in clinical practice. In the private practice of neurology and psychiatry, Fabing found that pipradrol has interesting clinical applications. These uses have since been extended into the field of general practice, in which pipradrol is useful in a number of common conditions.

The Use of Pipradrol in Medical Practice. The most important use for pipradrol is in the symptomatic treatment of emotional fatigue which usually occurs as a manifestation of a mild reactive depression.[5–9] There are no characteristic physical findings in such cases, but the patients usually complain of fatigue, and it becomes apparent from their history that they are unhappy and discouraged. Even the

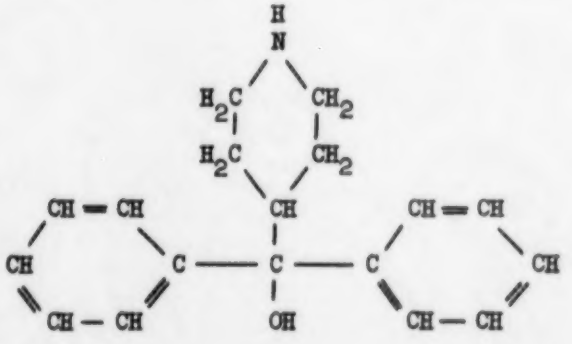

FIG. 2. Azacyclonol (Frenquel).

slightest task or decision requires too much effort. In relatively severe cases, the patient feels quite unworthy and expresses a pathetic sort of helplessness.

Social and economic readjustments associated with premature retirement and fear of aging are common causes of mild reactive depressions in elderly patients. The geriatric indications for pipradrol were first described by Pomeranze.[10] In patients of this type, relatively small doses of the drug (2 mg./day by mouth) are more successful than the usual dose of 6 mg./day commonly employed in other adult patients. At the low dosage level the patient is not consciously stimulated and may even feel that the doctor is not using an effective medication. This is best illustrated by the usual remark of the patient who states that the pills did not help and that it was unfortunate that he was a poor subject for the medicine, since he stopped feeling tired or unhappy shortly after his visit to the doctor. Because of the subtle nature of the action of pipradrol in geriatric patients, objective measurements were made[11] of a number of psychic and psychomotor functions, employing the usual double-blind method, in which neither the test subject nor the tester knew which patients were receiving pipradrol during one test period and the placebo during another. It was found that there are three measurable objective changes in which the performance of a group of normal men with an average age of 79 years was better during the period of pipradrol administration. The difference was statistically significant. These three methods depend on the ability of the subject to estimate an arbitrary period of time in which the error was about 35 per cent less during the pipradrol period than during the placebo period; strength of handgrip; and size of drawing of the human figure. The size of drawing of the human figure is a very interesting reflection of the subject's outlook on life. In optimistic persons who are well adjusted and content, the tendency is to draw larger figures than are drawn by persons who are pessimistic and withdrawn. The figures drawn during the pipradrol test period were bigger than those drawn during the placebo test period, and as with the tests of time estimation and hand strength, the difference was statistically significant.

Obstetric Use of Pipradrol. Obstetric patients are often subject to emotional fatigue and mild depression.[12] The symptoms may occur before or after delivery, and pipradrol is equally effective during both periods.

Use of Pipradrol as an Adjunct in the Dietary Treatment of Obesity. The use of pipradrol as an adjunct to the dietary treatment of obesity is potentially confusing, since the drug does not inhibit appetite. However, in a double-blind study[13, 14] it was found that obese patients are able to follow their diet better when receiving pipradrol than when receiving a placebo. This is reflected in a greater loss of weight. The difference is statistically significant.

Several explanations for this phenomenon have been proposed. One is that fatigue is a common result of caloric, and especially protein, limitation and that this is overcome by pipradrol, so that the patient is not tempted, instinctively or intentionally, to consume added food to overcome the sense of fatigue. Another explanation that has been suggested is that overeating is frequently the psychologic result of a depression; it ceases to express the patient's emotional upset after pipradrol has corrected the depression.

Pediatric Uses of Pipradrol. There are two conditions occurring in children in

which the general practitioner will find pipradrol useful. The first is in the group of behavioral disturbances in which the child is unable to live at peace with his environment and family, or in which he does poorly in school despite normal intellect.[16] In cases of this type the pipradrol dosage varies from 1 mg. to 3 mg. daily, and improved behavior can be expected in about one half of the children. In a few cases, behavior may become worse. The action of pipradrol in these children is, therefore, similar to that of amphetamine, but the advantage of pipradrol rests in the virtual freedom from insomnia and anorexia commonly produced by amphetamine.[16]

The second childhood disorder that is frequently helped by pipradrol is enuresis.[5] The dose is 1 mg. to 3 mg., and the drug is best administered late in the day or at bedtime. The aim is to give enough pipradrol to diminish the depth of sleep without preventing it. This varies from patient to patient, and it is therefore best to start with 1 mg. at bedtime, increasing the dose gradually until the desired response is obtained.

Use of Pipradrol in Chronic Disease. Emotional fatigue and mild depression are often associated with chronic disease and the convalescent period. In particular, patients with cancer and various neurologic disabilities are understandably discouraged and unhappy. Pipradrol has been extremely helpful in improving the outlook of such patients, although it can hardly be expected to have any effect on the course of the disease.

Use of Pipradrol in Alcoholism. There are many causes of alcoholism. In those cases where the patient drinks as a reaction to a depression, pipradrol is extremely useful.[15] It is, however, necessary to determine the cause of the drinking before the successful use of pipradrol can be predicted.

Drug-Induced Sedation. In addition to the fatigue and depression that can accompany almost any organic disease, there may occur sedation or drowsiness as a side effect of drugs.[5–7, 15] The most obvious examples are reserpine, the anticonvulsants, chlorpromazine, meprobamate, and the antihistamines. In patients who become drowsy or depressed from these drugs, pipradrol can be administered concurrently; it overcomes the drowsiness without interfering with the antihypertensive properties of reserpine or the anticonvulsant properties of drugs like diphenylhydantoin.

Neurologic and Psychiatric Uses of Pipradrol. Only occasionally will the general practitioner use pipradrol for the treatment of neurologic and psychiatric disorders. Somewhat larger doses than are recommended in the treatment of emotional fatigue and mild depression are frequently helpful in controlling narcolepsy, blepharospasm, and torticollis.[3, 4, 17–20] In the psychiatric field pipradrol is of limited value[21, 22] since the stimulation usually increases the pre-existing psychotic behavior. Ordinarily, this is undesirable. In psychotic depressions[3, 4] large doses of pipradrol occasionally produce dramatic results, but in general, electroshock treatment is preferable.

Side Effects of Pipradrol. In clinical dosage, pipradrol is virtually free from side effects. The early signs of moderate overdosage are nausea, vomiting, and insomnia.

A case of gross overdosage with subsequent recovery has recently been described.[23]

A young adult patient with suicidal intent took a single dose of 250 mg. of pipradrol (125 times the recommended single dose and more than 40 times the recommended daily dose). The patient of course was kept awake, and when first seen, appeared to be suffering from a reaction similar to chorea. She complained of apprehension and severe abdominal pain. Sodium Amytal, administered by mouth in repeated doses of 300 mg., did not influence the overstimulation caused by pipradrol. Symptoms were terminated by intravenous* Sodium Amytal in a dosage of 250 mg. Thereafter, recovery was uneventful; and liver and kidney function tests, as well as blood counts and urinalyses, revealed no toxic effects from the very unpleasant experience associated with such gross overstimulation. The patient is said to have indicated that in her next suicidal attempt she would employ a more pleasant drug!

Summary of Pipradrol Dosage and Indications. Pipradrol is administered by mouth. The tablets contain 1 mg.; the daily dose in children varies from 1 mg. to 3 mg./day. In adults, the usual dose is 6 mg./day although many patients respond favorably to 3 mg.; in geriatric patients the dose is 2 mg. given early in the day.

Medical indications are emotional fatigue and depression, for example as seen in geriatric patients, in obstetric patients, in the obese, in the chronically ill, in alcoholics, and in those who are depressed or sedated as a result of drugs.

AZACYCLONOL

The pharmacologic effects of azacyclonol in experimental animals were described by Brown et al[24] in March 1955. The characteristic stimulation produced by pipradrol in experimental animals can be inhibited partially by premedication with azacyclonol. With azacyclonol alone, there is a slight but measurable and statistically significant decrease in spontaneous activity of experimental animals. Fabing et al[25–33] and Himwich et al,[34–39] working independently, established that the characteristic action of azacyclonol in human beings is to correct hallucinatory and delusional disturbances. This occurs in some but not in all patients.

Importance of Antihallucinatory Drugs in General Practice. The three outstanding indications for azacyclonol are, of course, schizophrenia, toxic psychoses such as alcoholic hallucinosis, and postoperative confusion and delirium. Although, theoretically, patients with these illnesses should be referred to specialists for treatment, all three problems are of importance to the general practitioner and will increase in importance as more and more patients are discharged from mental hospitals to be controlled by maintenance doses of the various new drugs, one of which is azacyclonol.[40] The use of all of these new drugs is, therefore, of tremendous potential interest to the general practitioner.

Use of Azacyclonol in Schizophrenia. In schizophrenia, the primary defect is the inability of the patient to distinguish between the reality of his perceptions and conceptions that refer to the objective world around him and the basic unreality of the hallucinations and delusions through which he gains his knowledge of his autistic or psychotic world. As a result of responding in the objective world to his

* Barbiturates employed intravenously in treating gross overdosage should be used cautiously and symptomatically.

interpretation of his psychotic world, his behavior becomes inappropriate and psychotic. A drug that terminates hallucinatory and delusional activity interrupts the patient's contact with his dream world, leaving him only the surrounding objective world of reality. This can be accomplished with oral maintenance doses of 20 mg. of azacyclonol, three times a day over prolonged periods, in a substantial number of the schizophrenic patients who are treated within four or five years of the onset of their disease.[29, 38, 44–46] In patients who have been sick for a longer time, azacyclonol is occasionally effective, but the results are not so encouraging. However, many patients even of this type will be returned from mental hospitals to their community on maintenance doses of azacyclonol. In some cases a better effect will be obtained by adding one or more of the other drugs that have tranquilizing or antianxiety properties. All of these released patients will require medical supervision after they return to their community, partly to ensure that they continue to take their medication and partly to make certain that their behavior is sufficiently well controlled by the medication to permit social and economic rehabilitation.

Use of Azacyclonol in Alcoholic Hallucinosis. One of the most dramatic conditions responding to intravenous doses of 100 mg. of azacyclonol is alcoholic hallucinosis.[41–43] Patients suffering from this condition continue to see and hear things that are not there, even after they stop drinking. In almost all cases, these peculiar manifestations vanish within a few hours after the intravenous administration of a single dose of 100 mg. of azacyclonol. In some cases a maintenance dose of 20 mg., given by mouth three times a day, is desirable. There is evidence that continued administration of azacyclonol may relieve some patients of their desire for further drinking. This may possibly be the result of an antiobsessive or anticompulsive effect of azacyclonol in those alcoholics who suffer from compulsive drinking. Against this suggested explanation is the observation that, in general, the results of azacyclonol therapy have been rather disappointing in the treatment of most obsessive-compulsive states. Such patients usually do better following lobotomy than they do on azacyclonol therapy.

Use of Azacyclonol in Postoperative Confusion and Delirium. Postoperative confusion and delirium occur fairly commonly, especially in elderly patients who have undergone urologic surgery.[28, 29] The condition manifests itself usually on about the third postoperative day and is characterized by acute hallucinations and delusions. The patient may think, for example, that the container with parenteral fluids by which he is being fed intravenously actually contains snakes that are being infused into his circulation. To this he will naturally respond by hurling the bottle against the wall and ripping the needle out of his vein. Such reactions usually respond within an hour to the intravenous injection of 100 mg. of azacyclonol. The drug usually has to be repeated at intervals of eight hours for a period of several days. Oral maintenance dosage has not been explored fully since patients of this type generally recover after relatively few days, and the period during which they are treated is one in which parenteral fluids are usually being administered. It is convenient to add the parenteral solution of azacyclonol to the saline or dextrose infusion.

Dosage and Administration of Azacyclonol. The oral maintenance dose of azacyclonol

is 20 mg. three times a day. Initially this can be supplemented with intravenous azacyclonol given concurrently in a dosage of 100 mg. every eight hours for periods of up to several weeks if necessary. The intravenous route need not be employed; it serves merely to accelerate the response to oral azacyclonol which otherwise might be delayed in some cases as much as several weeks. A response has occurred, at least in 1 case, within an hour following the administration of the first 20 mg. tablet.

Side Effects of Azacyclonol. In the clinical dosage, azacyclonol appears to be virtually free from side effects. There is a suggestion[45] that in nonpsychotic patients there may be a slight sense of stimulation. Overdosage in psychotic patients seems to be free from side effects.

Summary of Azacyclonol Dosage and Indications. Azacyclonol is indicated in the symptomatic treatment of hallucinations and delusions associated with schizophrenia, alcoholism, and the postoperative state. Despite the use of a wide variety of doses by various investigators, it appears that 20 mg. by mouth three times daily may be adequate for maintenance therapy.[39] Azacyclonol can be administered parenterally early in the course of treatment, in which case it is given intravenously in a dosage of 100 mg. every eight hours. Concurrent administration of intravenous and oral azacyclonol is frequently helpful early in the course of treatment of schizophrenia. In patients in whom hallucinations are associated with alcoholism and the postoperative period, it is not always necessary to employ the oral maintenance dose. Many patients of this type respond favorably to a relatively small number of intravenous injections.

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Annual Meeting of the American Association of the History of Medicine

The 29th Annual Meeting of the American Association of the History of Medicine will be held in Durham, North Carolina, on April 19, 20, and 21. The meeting will be composed of two symposia and two general sessions.

The symposia are (1) History of Epidemiology and (2) The History of Medicine in the South.

Physicians desiring information on this meeting should communicate with Dr. George Rosen, Chairman, Columbia University School of Public Health and Administrative Medicine, New York 32, New York.

International Symposium on the Diencephalon

An International Symposium dealing with the relationship between the diencephalon and endocrine glands, organized by the Milan Section of the Italian Society of Experimental Biology, will be held May 3, 4, and 5 in the Sala delle Colonne of the Museo della Scienza e della Tecnica, Piazza S. Vittore 21, Milan.

The program will consist of presentations on the diencephalic control of endocrine activity, followed by open discussion on each topic.

For additional information write to Segretariato Symposium sul Diencefalo, Dr. S. B. Curri and Dr. L. Martini, c/o Istituto Farmacologia Università di Milano, Via Andrea del Sarto 21, Milan.

SPIRAMYCIN IN PULMONARY DISEASES. Acute pneumopathy due to pneumococci in 18 African Negroes has been successfully treated with Spiramycin. Defervescence occurred within 24 to 48 hours; within 15 days there was a total clearing of all symptoms in all patients.[1]

NATIONAL TUBERCULOSIS ASSOCIATION MEETING. Seven special lectures, eight panel discussions on pulmonary disease management, and 11 sessions of scientific papers have been planned for the fifty-first Annual Meeting of the American Trudeau Society, medical section of the National Tuberculosis Association, to be held in New York City's Statler Hotel on May 21 to 23. Dr. George Owen of Milwaukee, Wis., is chairman of the medical sessions program committee.

YELLOW FEVER INVASION OF MEXICO. Dr. Fred L. Soper, Director of the Pan-American Sanitary Bureau Regional Office of the World Health Organization, predicted that yellow fever would invade Mexico within months. Monkeys dead of yellow fever have been found in the Lake Izabal region of Guatemala, 75 or 80 miles from the Mexican border, and only 800 miles from the Florida Keys and Brownsville, Tex.

RESEARCH FOR COMMON COLD. At Johns Hopkins University in Baltimore, a study is being conducted to determine the role of psychologic factors in coryza. An attempt is being made to discover the mystery of why 30 to 50 per cent of colds are abated by medication as well as by placebos.

ORAL THERAPY IN DIABETES. Drs. Max Miller and James W. Craig of Western Reserve University report that clinical tests with an oral sulfonamide derivative, U-2043 (tolyl-sulfonylbutylurea), have been successful in lowering blood sugar levels. The new oral drug, most effective in the older, obese, stable type of diabetic, is being developed by The Upjohn Company under the name of Orinase.

VIRUSES DESTROY CANCER. Large quantities of APC viruses (adenoidal, pharyngeal, conjunctival) introduced directly into the site of the cancer can partially destroy cervical tumors, scientists at the National Institutes of Health in Washington report. Rapidly developing antibodies prevented APC's complete destroying action. Studies are now being made to prolong the viruses' effect.

NEW TB VACCINE. Dr. Guy Youmans, his wife Dr. Anne Youmans, and Dr. Irving Millman of Northwestern University Medical School, Chicago, have developed a new TB vaccine by grinding and spinning nonliving particles from live tuberculosis germs. The vaccine produced an immunity in mice equal to that found in immunization with BCG.

WORLD MEDICAL ASSOCIATION MEETS. The Council of the World Medical Association will be convened in its twenty-sixth session in Cologne, Germany, April 29 to May 5, 1956. The 1956 General Assembly will be held in Havana, Cuba, October 9 to 15.

MORTALITY RATE DECLINES. From 1940 to 1950 the United States saw the most significant decline in the death rates for older people and a continuation of the marked decline in mortality for those in the younger ages which has prevailed since 1900. According to the Health Information Foundation, nearly 400,000 people of all ages would have died in 1950 had the mortality rates of only 10 years earlier prevailed.

NUCLEAR STUDIES. The Oak Ridge Institute of Nuclear studies has announced a four week advanced medical course, which will be offered to physicians in separate one week units this spring, summer, and fall. Information and application blanks may be obtained by writing to Dr. Ralph Overman, Chairman, Special Training Division, Oak Ridge Institute of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn.

SYMPOSIUM ON ANTIBIOTICS. The Fourth Annual Symposium on Antibiotics, sponsored by the Food and Drug Administration, Division of Antibiotics, of the U. S. Department of Health, Education, and Welfare, and the journals ANTIBIOTICS AND CHEMOTHERAPY and ANTIBIOTIC MEDICINE AND CLINICAL CHEMOTHERAPY, will be held on Oct. 17, 18, and 19, 1956 at the Willard Hotel, 14th Street and Pennsylvania Avenue, N.W., Washington, D. C. Manuscripts should be submitted to Dr. Henry Welch, Director, Division of Antibiotics, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D.C., by Sept. 17, 1956.

PHYSICAL THERAPISTS CONVENE. Mildred Elson, president of the confederation and executive director of the American Physical Therapy Association, 1790 Broadway, New York City. has announced that physical therapists and other health specialists from more than 20 countries will confer on world-wide rehabilitation problems and progress during the Second Congress of the World Confederation for Physical Therapy at the Hotel Statler, New York City, June 17 to 23.

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Psychobiology and Drugs

The admirable survey of tranquilizing agents presented in this issue of INTERNATIONAL RECORD OF MEDICINE once again raises that perennially absorbing question of whether the chicken or the egg has priority in the biologic sequence of life. Since the remarkably rapid rise of pharmacologic treatments for neuropsychiatric disorders, the question should now be put in more modern terms, namely, in what way do psychologic disorders effect physiologic changes in the nervous system or, conversely, in what way do physical changes in that system produce psychologic manifestations?

It is, of course, elementary knowledge that a close relationship exists between structure and function in biologic processes. The glandular cells cannot be separated from their secretions any more than muscle cells can be divorced from contraction; nerve cells are inseparable from their ability to conduct impulses. But for centuries the belief persisted that there was some unbridgeable gulf between mind and matter, between emotion and biochemistry. Most of the followers of Freud (in contradistinction to Freud himself), until recently, were not eager to admit the possible origin of psychoses in metabolic disorders. Drugs were recognized as sedatives and hypnotics, but no more.

Within the last few years, with dramatic suddenness, psychiatrists, neurologists, and biochemists have had what has been termed modernized "psychobiology"* thrust upon them. As some of the papers published in this issue show, every new tranquilizing drug brings forth discussion of hypotheses on its mode of action and on the etiology and pathogenesis of psychoses. One of the most fascinating of these is the possibility that some natural derivative of adrenal gland secretion is responsible for producing psychotic states. The pioneering work of the Creedmoor group[1] laid one of the earliest integrated foundations for this very same hypothesis and attempted to uncover the common physiodynamic features of the therapies then in use.

Epinephrine is known for its prompt appearance on almost all occasions when the body is subjected to emotional stress, fear, anger, grief, or just plain everyday worry. Its chemical molecules invade tissues and fluids, playing havoc with the normally balanced organism. Epinephrine also has drawn the suspicion of biochemists by its notorious instability, its deterioration into quinones and other products of decomposition. Adrenochrome is such a product, and when this finds its way into the blood stream of human beings (Hoffer et al[2]), it produces quite startling psychic turmoil akin to the effect of mescaline. The latter, incidentally, is also chemically related to epinephrine, and is the active principle of the *peyote* (*Anahalonium lewinii*),

* "Psychobiology" in the light of recent advances was discussed in the editorial, "The Great Physiodynamic Therapies in Psychiatry" by Félix Martí-Ibáñez, Arthur M. Sackler, Mortimer D. Sackler, and Raymond R. Sackler, published in the *Journal of Clinical and Experimental Psychopathology & Quarterly Review of Psychiatry and Neurology*, vol. 17, page 1, January-March, 1956.

so much favored by Navajos and other primitive tribes in their orgies of drug-induced hallucination and frenzy.

Adrenochrome is an indole derivative, possibly formed in the metabolism of adrenalin by amine-oxidase. What is curious, as Dr. Fabing points out in his paper, is that so many compounds having an indole or similar nucleus produce peculiar effects in the central nervous system; these include alkaloids such as those of harmala, yohimbine, ibogaine, voacangine, and lysergic acid diethylamide; by stretching the similarity one could even include cocaine, scopolamine, and caffeine.

Another intriguing aspect of psychochemistry is the discovery that a compound such as 5-hydroxytryptamine can produce psychic changes. This "sympathomimetic amine" is a normal constituent of body tissues and fluids. As Woolley and Shaw[3] have suggested, it is perfectly feasible that if for some reason the metabolism of 5-hydroxytryptamine is interfered with, it may accumulate sufficiently to cause symptoms resembling schizophrenia and other major psychoses. It is also not at all improbable that an adrenal substance such as adrenochrome, accumulated through an abnormal metabolism of epinephrine, may in turn compete with the enzyme systems involved in the metabolism of 5-hydroxytryptamine and thus touch off a somatopsychic chain reaction.

With the latest knowledge at our command it is not wildly fanciful to foresee a time when all the links in the chain will be forged into solid connecting links. The controversy over the priority of the psyche or soma will then have become historical and academic. Metabolic psychiatry might well be the psychiatry of tomorrow. Psychobiology will then be a solid pillar of medicine.

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The Medico-pharmaceutical Arts of "La Celestina"

A Study of a Fifteenth Century Spanish Sorceress and "Dealer in Love"

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SPANISH MEDICINE IN THE FIFTEENTH CENTURY

In the history of Spain, the fifteenth century marked the opening of the gateway through which the Spanish people sailed forth to become a decisive factor in the progress of Western civilization. Up to the end of that century, which is to say, until the dawn of the Golden Age in Spain, Spaniards were busy demolishing the last Moorish outposts on the Iberian Peninsula, laying the foundations of national solidarity through the union of the kingdoms of Aragon and Castile, conquering Granada, and discovering the New World.

From a medico-historical point of view, the fifteenth century was a period of transition attendant to the integration of Byzantine medicine, which was to be re-established in Spain after the fall of Constantinople in 1453, with Arabian medicine.

In this century of the discovery of the New World, against a motley and picturesque scene stirred by the winds of conquest and already lighted by the lamps of new cultures, there prevailed on the Iberian Peninsula a coalescence of the learning of three groups of Spanish physicians: Jewish, Moslem, and Christian.

The medicine of this period was concocted from the varied contributions made by these streams of culture. From the Jews was derived a penchant for Hippocratic principles, a taste for astrology and cabalism, the practice of medical teaching by word of mouth, and a leaning toward dramatic display; from the Moors—invaders of Spain since the Battle of Guadelete—were imbibed the diehard tendencies of Latinized Hippocratic tradition, a multifaceted culture, naturalistic trends, alchemy, and physiotherapy; and the Christians contributed theologic and mystic strains of clericalism, ceremonialism, and a fondness for anatomy and pathology based on their supernatural concept of the Universe.

The lamps of learning lighted in the thirteenth century by the renowned colleges of translators in Toledo, which revived Greek and Roman medicine, were still burning. Spanish, the golden tongue of soldiers, mystics, philosophers, and poets, the beautiful, heroic language of Castile, now became a channel for the conveyance of medical learning.

Universities had been flourishing in Spain since the year 1214. Since 1240, a Chair of Anatomy had existed in Valencia and another in Lerida since 1391, one of the first colleges in Europe to sanction the practice of necropsy. Toledo was the hub of Arabic-Spanish culture. It was there that Gerard of Cremona and Michael Scotus were to cement their reputation.

From 1474 onward a printing press was in operation in Barcelona, where, at the beginning of the following century, in 1514, the first polyglot Bible was published

by the Theological Faculty of the University of Alcalá; its Greek and Hebrew texts, together with a complete critical appendix, glossary, and grammar, represented in the words of a chronicler in 1844 "the first truly scientific work of the Modern Age."

The heritage of Séneca, of St. Isidore of Seville, of the Caliphate of Córdoba, of Maimonides, the labors of the Benedictines of Cluny and of Alphonso VI, the erudition of the universities of Valencia, founded by Alphonso VIII in the twelfth century, and Salamanca, founded by Alphonso IX in the thirteenth century, the scholarship of the Academy of Medicine founded by Alphonso X in 1255, the results of experiments in the pesthouses and leprosoria established in the time of Rodrigo Diaz, the Cid Campeador, all the abstruse medical knowledge gathered by Arnaldus Villanovanus and Raymond Lully in Catalonia dating from the thirteenth century, the field hospitals established by Isabel II, the College of Surgeons at Valls near Barcelona, the achievements of Doctors Gaspar Torruella and Villalobos—all these formed the richly colored warp into which was woven the empirical medical knowledge of the fifteenth century.

As in every period preceding a new age, confusion and disorder were rife. The physician from his watchtower peered at a horizon so wide and crowded that he was distracted from the proper contemplation of the purely medical landscape. The empiricism prevailing in sundry branches of medicine spread to all medicine, particularly to therapy, in the Peninsula. As a reaction against the exuberance of Arabian polypharmacy there began a return toward phytotherapy and doctoring with herbs and simples. The masses, however, remained partial to the balms and comfits, pills and syrups concocted by the bounteous hands of the Arabs.

The *Libre apellat Macer*, written by an unknown author, still preserved in the Archives of the Barcelona Cathedral, comprises innumerable references to botanical medicine, grammar, astrology, mystic devotions, and incantations, all jumbled together and topped by a treatise on the art of cooking.

Another folio, author unknown, printed in Burgos in 1495, entitled *Epílogo en medicina y cirugía conveniente a la salud* ("A Sequel on Medicine and Surgery Conducive to Health"), contains a farrago of astrology, pathology, physiognomy, surgery, urinalysis, and bloodletting.

It would appear, therefore, that the fifteenth century, with its protean ramifications, was a well fertilized field in which quackery could flourish. In this vast jungle of spellcasting and sorcery there stands out as a pattern for all time the figure of a little old hag, a dealer in love and lechery, a winebibbing go-between, with a full stock in trade of traditional ignorance and wizardry to make her truly typical of the quackery of the period. This bent old woman, whose trotting footsteps rouse faint echoes in the ancient alleys of Toledo, was the notorious Celestina.

HISTORICAL PROFILE OF CELESTINA AND OF HER CREATOR

The hidalgo Fernando de Rojas (?–1541), the much discussed author of *Celestina*, was born in Puebla de Montalban, a small village on the outskirts of Toledo, and practiced as a lawyer in nearby Talavera, where for several years he held the position of mayor. He married, raised a family, and died—all in his birthplace, being buried there in the Church of the Convent of the Virgin. But his monotonous existence

Woodcut from the first edition of *Epilogo en medicina y cirugia conveniente a la salud* (Burgos, 1495).

was enlightened by one creative period that raised him out of the rut of respectable mediocrity to the dizzy heights of immortality. This period lasted only fifteen days (some say fifteen years), which is what it took him to write his immortal "Tragicomedy of Calixtus and Melibea" or *La Celestina*, inspired by his readings of Petrarch, Boccaccio's *Fiammetta*, and the works of Juan Ruiz, better known as the Archpriest of Hita.

La Celestina or *La tragicomedia de Calixto y Melibea*, of which not a single copy of the first edition has yet been found, was reprinted in Burgos in the year 1499. The only copy extant of this second edition is in New York in the library of the Hispanic Society of America.

The original work, in twenty-one acts, is supposed to have been written in 1483 or 1497. *La Celestina* surpasses in tragic strength and realistic conception everything that went before it in Spanish literature of this class; it was the first book in Spanish to spread throughout Western Europe and to enjoy universal popularity during the sixteenth century. Rojas' pellucid prose style gave literary embodiment to popular speech and inaugurated the artistic renascence in Spain. It is a drama of passion in which the youth Calixtus, to obtain the favors of the beautiful maiden Melibea, enlists the aid of the aged and crafty go-between Celestina and by such means eventually wins the maiden to his lusty will.

Whether or not the old crone was based on a real character actually known to the author has been a matter of much discussion. The famous Portuguese writer Amato Lusitano (Juan Rodriguez of Castello Branco), who completed his studies at Talavera University in 1529, in his celebrated medical treatise refers to the actual existence of Celestina (this was quoted by Menéndez Pelayo in his "Historical Sources of the Spanish Novel"). Lusitano, in his commentary on Dioscorides (In: *Dioscoridis Anazarbei de materia medica libros quinque e narrationes eruditissimi Doctoris Amati Lusitani. Venetiis, apud Gualterum Scotum*, 1553, lib. III, p. 1907), mentions an animal glue factory located in Salamanca, close to the Tormes bridge, "not far from the home of Celestina, a notorious wise woman appearing in the comedy of Calixtus and Melibea" ("*Non procul a domo Celestinae mulieris famosissimae et de quale ajitur in comedia Calisti et Malibeae*"). Dr. Pedro Diaz also mentioned this quotation in 1895 in his *Archivos da Historia da Medicina Portugueza*.

A later reference to the actual existence of this female quack appears in *El peregrino curioso* ("The Inquisitive Wanderer"), by Bartolomé de Villalba y España (1577), to the effect that certain students showed him Celestina's home near the tan pits.

Sancho Muñón, who plagiarized Rojas' work, in his *Tragicomedia de Lisandro y Roselia* ("Tragicomedy of Lysander and Roselia") also alludes to Celestina as dwelling in those parts and to the fact that the tomb of this archetype of quacks and bawds is to be found in St. Lorenzo.

SILHOUETTES OF CELESTINA AND HER TEACHER CLAUDINE

When Rojas first presents Celestina, she is seen traipsing through the narrow alleys of Toledo, over which coveys of pigeons are in flight while the church bells are tolling. She is carrying a pitcher of wine in her shaking hands. Inquisitive feminine eyes behind the shutters follow her progress. The convent bells are ringing

like the beating of a happy heart. Celestina walks circumspectly, greeting here and there a blushing priest who some while back may have been one of her clients. All the while she pries here and peers there into everything in sight. Sixty years of roguery are heavy on her shrunken shoulders. A crafty smile hovers on her lips, withered and faded like an autumn leaf.

A small boy playing in a doorway shouts "*¡la barbuda!*" (Hey, Whiskers!), and at the sound of this tribute to her hirsute countenance the old crone threatens to box the ears of the young imp who, however, continues to yell after her until she finally disappears from view. Shrugging her shoulders, she tramps on with the pitcher of wine in her hand, spilling a crimson drop here and there as she stumbles over the stones of the unpaved street. She is neither good nor evil. She defies all classification. If people call her *satánica* (devilish), it is because they do not know that in her past there is a bitter tale of woe and that the knife slash across her face is a relic from a lovers' quarrel, a scar that all her magic art could not heal.

Meantime, her past life rustles through her mind like leaves in the fall. Her weary feet now follow the slope of the roadway, bathed in the golden glow of a topaz-colored sunset. She remembers how she plied her trade. By the river, near the tan pits and leather yards, is her ramshackle hut, which in itself is sufficient to strike awe into visitors. She goes through the sagging doorway, forever ajar. Her bony hands, glimmering like the bronze of a lamp, move deftly. She shakes off her heavy cloak, drops onto a stool, gets up, thinks back on her past renown and the rewards thereof which are now gone like autumn leaves before the October wind.

Celestina, full of woe and sentimentality, steps outside to take a breath of the fresh evening air laden with the scent of flowers and the pungent odor of drying hay. Her glance wanders toward the river rippling in the distance, seeing in her mind's eye the glossy hides, shining like silver shields in the moonlight, hung out to dry by the placid waters. The cool breeze now caresses her face, wizened and yellowed like ancient parchment. In her boundless solitude, she becomes lachrymose, while the somber poplars near the river's edge lean toward her, their foliage drooping like tresses from the head of a sorrowing woman.*

When we meet Celestina, she is sixty years of age, she claims, but her crony Parmenus tells that the old dame has already seen "two-and-seventy summers." Despite her senile hairiness, which begot her the nicknames "*vieja barbuda*" ("Old Mother Bigbeard") and "*la barbuda*," her countenance was probably not unpleasant, for she always wore a crafty but friendly smile. Besides, she was not averse to using on herself the cosmetics that she concocted for her clients, including that antimonial stain beloved by Syrian women that puts a sparkle in withered pupils and dilates their size. This is what Parmenus alludes to when he calls her a "coal-eyed old lady," a phonetic pun on *kohl*, Arabic for antimony.

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* Celestina, who is first described in the extravagant words with which Sempronius tells his master, Calixtus, of her trade and tricks, is a little old woman whose namesake appears in the play *Libro del esforzado caballero Don Tristán de Leonis* ("The Book of the Brave Knight Sir Tristam of Lyons"), where "the tale goes that when Sir Lancelot was parted from the maid, she gathered unto her many people, among whom was her aunt Celestina."

According to her own story, Celestina had been a girl of great beauty, the youngest of four children, but as the result of a dissipated girlhood she had aged rapidly, her wizened face made uglier by a long knife scar.

To the effects of her tempestuous career must be added the influence of her teacher, Claudine, with whom she was hand-in-glove, perhaps united to her by Lesbian ties, a theory supported by her lustful propensities and her statement, ". . . from her [Claudine] I learnt all the choicest there was to know of my trade . . . we ate together, slept together, took our relaxations in one another's company and our pleasures and counsels in common" ("*Della* [de su maestra] *aprendí todo lo mejor que sé de mi oficio . . . juntas comíamos, juntas dormíamos, juntas aníamos nuestros solazes, nuestros plazeres, nuestros consejos y concierto*").

Claudine's lover, an alcoholic, possessed a virile bearing, which may indicate the manner in which she influenced Celestina's love life. Meaningful are the words Celestina uses when bewailing her friend: "Oh, how sweet she was! How gentle, clean and virile!" ("*¡ O qué graciosa era! ¡ O qué desembuelta, limpia, varonil!*").

The aged Claudine practiced sixteen years as a midwife, a profession that cloaked her pandering activities and allowed her to come and go wherever she chose without arousing suspicion.

To her prowess as quack and procuress, Claudine added sorcery, since in those times every medicaster practiced magic in order to acquire supernatural powers and to stand on a pedestal of awe above the people. As a result of all this, the Inquisition hauled her up four times, once together with Celestina. On one occasion she was denounced as a witch—perhaps the deadliest accusation possible in the Middle Ages—because she was caught "gathering earth by candelight in the dead of night at a crossroad" (in those days a place of execution or a burial ground), and was sentenced to stand in the pillory before the populace with a conical cap on her head. That such accusations were well founded is shown by the words of her disciple: ". . . she went from graveyard to graveyard in the dead of night as easily as by day, seeking the tackle for our trade. There was not a single Christian, Moor or Jew whose funeral she did not attend. She lay in wait for them by day and dug them up by night. With her tweezers she filched seven teeth from a hanged man's mouth, while I took off his shoes. . . . What more for me to say than the very devil's imps themselves were afraid of her? She kept them in awe and terror by the bitter words she flung at them . . ." ("*. . . se andaua a media noche de cimenterio en cimenterio, buscando aparejos para nuestro oficio, como de día. No dejaba cristiano, ni moros ni judíos, cuyos enterramientos no visitara. De día los acechaua, de noche los desenterraua. Siete dientes quitó a un ahorcado con sus tenacicas de palacejas, mientras yo le descalcé los zapatos. . . . ¿Qué más quieres sino que los mesmos diablos la hauían miedo? Atemorizados e espantados los tenía con las crudas bozes que les daua . . .*").

Old Claudine died from her many excesses, particularly alcoholism, for as her follower says, ". . . she never came back without gulping down eight or ten draughts, a pint in the jar and the other inside her" ("*. . . jamás bolbia sin ocho o diez gostaduras, un acumbre en el jarro e otro en el cuerpo*"). From her, Celestina got her taste for liquor and the pleasures of the table, as well as her bent for sexual debauchery. She explored all the pathways of erotic excess. In a dialogue with her godson Parmenus, she

cueze el pan: teme tu negligẽcia: maldize ſu auaricia
ꝛ cortedad: porq̃ te dio tã poco dinero. Ce. no es co-
ſa mas ꝓpia del q̃ ama q̃ la impactẽcia: toda tardãça
les es tormẽto: niguna dilacio̅ les agrada. en vn mo
mẽto q̃rrian poner en efeto ſus cogitaciones: antes
las q̃rrian ver concluydas q̃ empeçadas: mayormẽte
eſtos nouicios q̃ contra qualq̃era ſeñuelo buelã: ſin
deliberacio̅: ſin penſar el daño q̃ el ceuo de ſu deſſeo
trae mezclado en ſu exercicio ꝛ negociacio̅: para ſus
ꝓpones ꝛ ſiruientes. Sẽ. q̃ dizes de ſiruiẽtes pareſce
por tu razõ q̃ nos puede venir a nos otros daño dſte
negocio: ꝛ q̃mar nos cõlas centellas q̃ reſultan deſte
fuego de caliſto. avn al diablo daria yo ſus amores:
al primer deſcõcierto q̃ vea eneſte negocio no como
mas ſu pã: mas vale ꝓder lo ſeruido q̃ la vida por co-
brallo: el tꝑo me dira q̃ faga: q̃ primero q̃ cayga del
todo dara ſeñal como caſa q̃ ſe acueſta: ſi te pece ma-
dre guardemos nras ꝓpias de peligro: faga ſe lo q̃

Full-page reproduction from the second edition of *La Celestina*, printed in Burgos in 1499. (Through the courtesy of the Library of the Hispanic Society of America, New York.)

says: "Do you remember, dear boy, when you used to sleep at my feet?" ("*¿Acuerdaste cuando dormías a mis pies, loquito?*"). To which he replies: "Yes, indeed I do! Sometimes, even though I was then but a child, you hoisted me on to the bolster and pressed me close to your bosom, but you smelt so old I used to run away from you!" ("*Sí, en buena fe. En algunas veces me subias a la cabesera y me apretabas contigo, e porque olías a vieja, me fuya de ti . . .*").

Great was Celestina's vogue in Toledo. In the history that Parmenus tells his master, we can see, even after allowing for all possible exaggeration, the great fame that the old woman enjoyed, a fact easily explained by the very strait-lacedness that ruled the town and that made every rumor and tale spread like wildfire under the irresistible seal of "it's a secret." In the words of Parmenus: "She is the subject of conversation at all gatherings, meetings, merrymakings, weddings, feasts, burials and occasions of intercourse . . . the woodworkers sing her praises, the woolcombers, weavers, gardeners, field-laborers and vine-tenders rule their daily round by her counsels . . ." ("*En los convites, en las fiestas, en las bodas, en las cofradías, en los mortuorios, en todos los ayuntamientos de gentes, con ella pasan tiempo . . . cantanla los carpinteros, peynanla los peynadores, texedores, labradores en las huertas, en las aradas, en las viñas, en las regadas con ellas pasan el afán cotidiano . . .*").

Her greatest claim to fame, however, was among the priests and clergy, who made up the most important section of the community. She herself says her trade was "the sale of concubines" to priests. Thus, in her declining years, she is able to recall with zest the days of her prime when her house was crammed full of "old gents and lads, church-folk of all ranks from bishops down to sextons" ("*caballeros viejos o moços, abades de todas dignidades desde obispos a sacristanes*"), who presented her with all kinds of gifts: "many fowls, chickens, geese, ducks, partridges, turtle-doves, hams, suckling-pigs, wheat cakes and fine meal loaves" ("*muchos pollos, gallinas, ansarones, anadones, perdices, tórtolas, perniles de tocino, tortas de trigo, lechones, bodigos*"), as well as wine in abundance—the fine red wine of Mondiego, Luque, Toro, Madrigal, St. Martin, and other districts—which she sampled modestly enough to begin with but ended up by gulping down by the bucketful.

THE PASSION FOR WINE

These offerings were a great satisfaction to Celestina, for though in her old age she was circumspect in eating (she could exist for three days on a hunk of bread soaked in wine, reinforced by innumerable swigs from the wine bottle), neither at table nor in bed would she forego her pitcher of wine to warm her blood and sustain her in a condition ever ready for business. Wine for her "drives depression from the heart, puts color into wan cheeks and courage into the coward, comforts the brain, shifts cold from the belly, dispels stench from the breath, sweats out all evil humors, clears out head colds and toothache, and prevents nausea" ("*. . . quita la tristeza al corazón, pone color al descolorido, coraje al cobarde, conforta los cerebros, saca el frío del estómago, quita el hedor del aliento, hace sudar toda agua mala, sana el romadizo e las muelas, sostiene sin heder en la mar*"). For all these reasons, she always gulped a dozen draughts at every meal except if invited out, when, of course, she took a double dose.

In her eulogy on wine, we cannot fail to note the empirical equivalent of the cures by alcohol introduced by the Moslems in Spain and popularized there by Moorish physicians, such as Avicenna, who not only recommended such remedies but were themselves great patrons of old wine. All medicine in fifteenth century Spain embraces this reliance on the curative virtues of alcohol, which occurs in all empirical medicine.

Celestina's passion for drink is a characteristic frequently found to a greater or lesser degree in all charlatans.* The Dipsas or Pythonesses and go-betweens mentioned by Ovid became what they were through their unquenchable thirst and not from a lack of water either! A similar passion afflicted Laena, the doorkeeper of the Cistellaria in Plautus' "Curculio" (Master Weevil the Parasite). The word "dipsomania" is derived from the name of the inebriated Dipsas. Perhaps Celestina herself was not many stages removed from this type of psychiatric disorder. Hence, in the play we find her so frequently, wine pitcher ever to hand, wending her way with stumbling steps through the streets of Toledo.

THE POLYFACETIC ACTIVITIES OF A SORCERESS

Celestina owed a great deal of her reputation to her multifarious activities. Diversity in operations was a characteristic of quacks and sorcerers, who kept many irons in the fire at one time. Unlike the physician, the quack needed to create for himself not a science but an *atmosphere*. What he actually did was not so important as *what people thought* he could do.

Talking of Celestina, Sempronius says she is a "a sorceress shrewd and cunning in everything relating to the Black Art. I have been told that the number of spells she has cast or reversed in the town amounts to well over five thousand. She can awaken lust in stones if need be! " ("*Hechicera, astuta, sagaz, en cuantas maldades hay. Entiendo que pasan de cinco mil componendas las que ha hecho y desecho en la ciudad. A las duras peñas promouerá e prouocará a la luxuria si quiere*"). We then may deduce that she was a witch—a perilous profession in the days of the Inquisition—and that she acted as a lovers' go-between, supplying them with aphrodisiacs to excite their passion (for which purpose she needed only to fall back on the vast armory of aphrodisiac drugs then in existence) and afterwards repairing any physical damages resulting therefrom. According to her former retainer, Parmenus, Celestina is "seamstress, perfumer, past-mistress in the concoction of cosmetics and in patching up the troubles of maidens, also a procuress and something of a witch" ("*. . . labrandera, perfumera, maestra de fazer afeite e de fazer remiendos virginales, alcahueta e un poquito hechicera*").

The profession of seamstress was nothing more than one of the fronts adopted by all charlatans to evade the eyes of the law and as an excuse to go everywhere without difficulty. Moreover, such a trade enabled Celestina to leave her door

* Shakespeare often praised Spanish wines. His Mistress Quickly, the English Celestina, remarks to Doll Tearsheet (Henry IV, Act II, scene iv): "But, i'faith, you have drunk too much canaries [wine of Canary Islands], and that's a marvellous searching wine, and it perfumes the blood ere one can say: What's this?"

open to maidens, students, and priests, and to enter other people's houses, for though she sometimes called herself a "child doctor," lechery more than pediatrics was her principal means of livelihood. In addition, she spun worsted, wrote doggerel and hymns for the monasteries, concocted perfumes, drugs, ointments, pastes, pomades, rinses, powders, and lyes; she also sold medicinal herbs, cosmetic oils and balms, and possessed moreover the surgical skill already alluded to.

THE DWELLING OF A FIFTEENTH CENTURY "WITCH"

Celestina lived, as was the custom of such soothsayers, who paid the greatest attention to the aura surrounding them, on the outskirts of the town (Toledo or Salamanca) where her creator Rojas set the scene. Her dwelling lay "by the riverside," near the leatherworks or tan pits, which in every town were situated in small bystreets on the river banks. Hers was an ancient shack, half in ruins, poorly furnished, "and worse provisioned," all factors of great importance in the art of soothsaying. It would be inconceivable that Celestina should sell her balms or weave her spells anywhere else than in such a shack, crammed full of concoctions and nostrums concealed behind cupboard doors and discreet lattices.

On entering, the visitor's nose was immediately assailed by a bittersweet odor in which the gentle perfume of amber mingled with the pungent scent of musk and civet. Glass retorts and phials and casks of tin and clay of all shapes were strewn everywhere. The tables were littered with pots of ointment, silver pomanders, balls of wax, jars of mercury, storax, philters, musk perfumes, pomades and lotions to put a bloom on the face, bottles of bleaching lotions and essences of rose and other petals, bits of asphodel root, bladder senna, goat's horn, oak galls, mistletoe, and various distilled and sweetened liquors. Dressed hides and skins lay about, and preparations such as lime water containing powdered jalap root or marrow from the bones of fallow deer and heron were also on hand, together with pot-bellied glass jars containing sweet-smelling solutions of rose, orange blossom, jasmine, clover, honeysuckle, and powdered cloves distilled in wine or rectified spirit, lyes and dyes made from henna to bleach the hair or restore its color, vine shoots, swamp oak, ergot, and alum. And there were rows upon rows of jars of salves and pomades containing, according to Celestina, extracts from cow, bear, horse, rabbit, camel, hare, whale, fallow deer, bearcat, badger, squirrel, hedgehog, and otter, but which most likely were all of the same composition, although each one was colored differently from the rest.

From the roof hung packets and sheaves of all kinds of herbs for the preparation of medicinal baths: camomile, rosemary, elderberry, marshmallow, maidenhair, melilot, mustard seed, lavender, white laurel, dog rose, couch grass, wildflower, thorn apple, silvertongue, and sepia flake. The study from a pharmacologic angle of this impressive array of herbs should indeed afford a good idea of the state of physiotherapy in that age.

There were also small earthenware pots containing facial oils and essences made of storax, jasmine, lime, violet, benjamin, pistachio, pine kernels, melonseed,

jujube, fumagine, lupine, vetches, sea holly, and chickweed, vials of balsam for healing scratched noses, and little boxes containing bits of bladder.

In one corner—and here we follow the detailed "stage directions" in the play—stood a small platform on which lay a painted vessel, some long thin needles such as those used by weavers, and waxed silk thread, while overhead hung roots of spikenard, red sumac, squills, and horsetail—all of which was evidence of her ventures into surgery.

But of all this, the most awe-inspiring and even frightening sight was the room where she concocted her potions for purposes of sorcery and the treatment of love sickness. Here were weird-looking skins and membranes, bones, hearts of stags, adders' tongues, heads of quail, asses' brains, haircloths, horses' hides, cauls, loincloths, black beans, a lodestone, the inevitable hangman's rope, ivy leaves, hedgehogs' quills, badgers' feet, fern seeds, a stone from an eagle's eyrie, and many other items among which, of course, there was no lack of wax hearts pierced with pins and awful little effigies in clay and lead. Examining the symbolism and potentialities of all this gallimaufry of soothsaying, we find the same superstitious usages as were rampant among primitive tribes when the witch doctor claimed to cure pain and even death by the magic virtue of his fetishes.

Perhaps Celestina's infernal apparatus did indeed work miracles. For when the client emerged from that horrendous hovel, he must have delighted in breathing once more the fresh wholesome air and the overriding aroma from the hay fields, and in hearing the whispering Tagus, "Knight and Crusader," while his gaze wandered happily across the cerulean blue of the lofty Toledan skies.

CELESTINA AS A SORCERESS

Despite many allusions throughout the play to Celestina's witchcraft, and Menéndez Pelayo's description of her as "the spirit of evil incarnate in a vulgar and uneducated creature possessing nevertheless intelligence and cunning," and Julio Cejador's observation, "In Celestina there is definite deviltry, she is a true sorceress but no trickster," this does not appear to be the dominant activity in her. The main thing about a witch is that she should believe in her own spells, but for Celestina a spell was merely an adjunct to medicaments or to her panderings to debauchery. True, she did cast a large number of spells, but then charlatans in all ages have done that, either from conviction or to make the most of the credulity of the masses.

In the spell she casts in Act III, before she starts her campaign on Melibea—this being the normal procedure in all performances of magic—she puts herself on a plane of equality with the devilkins she is invoking, using at once threats and cajolery to bring them to heel. But this spell (so different from that practiced in front of the cauldron, where their exotic nostrums are cooking, by the witches in Shakespeare's *Macbeth* (Act IV, scene i)) seems in her case to be more of a play to the gallery and a means of reinforcing her plans than a real spell on whose efficiency she relies.

For Celestina, such a spell is almost a ritual when commencing operations in

amorous affairs. In the presence of Sempronius, the servant of her client Calixtus, she purposely calls out to her maid Elicia the whole awe-inspiring list of the magic ingredients she needs, doing this in their presence in order to obtain their greater obedience and to show off her prowess. She therefore instructs Elicia to go upstairs where she keeps her most secret paraphernalia and to bring down "the can of snake-oil, I mean, the compost of adder's venom" ("*el bote del azeyte serpentino o sea aceite compuesto con ponzoña de víboras*") which, she adds, is next to the hangman's rope she filched from the gallows one dark and stormy night. She bids the girl to open the heddle chest in the attic (which indicates that our sorceress lived in a home formerly inhabited by weavers, who always kept such a chest in the attic) and to take out the sheet of paper written "in bat's blood" lying "under that dragon from the wing of which we pulled the nails" ("*debaxo de aquel ala de drago a que sacamos ayer las uñas*"). And she admonishes the girl while still up there not to upset the May-day rain water which had been brought in for some concoction. All these paraphernalia pertain to witchcraft, and even Pliny in his time mentioned them as popular remedies against all ailments.

She tells the maid to go into the ointment room where she will find what she is looking for "in the black cat's skin, where I told you to fix the she-wolf's eyes" ("*en la pelleja del gato negro, donde te mandé meter los ojos de la loba*"), and orders her to bring down also "the billy-goat's blood and a few of the hairs you snipped from his beard" ("*la sangre del macho cabrío y unas poquitas de las barbas que tu le cortaste*"). Bits and scraps like these serve to show the magical value which at that period was set on such relics as well as on certain animal therapy, so common in the Middle Ages, which later became known as "garbage pharmacy" ("*botica de las inmundicias*"). In all her activities, we recognize in Celestina a clever woman who knew how to exploit to the full the rich vein of popular superstition.

CELESTINA'S COSMETIC, PHARMACOLOGIC, AND MEDICAL KNOWLEDGE

Generally a quack's wisdom had roots different from those of the true man of science. The former based his knowledge on direct naturalistic observation of the symptoms displayed before him. If several persons affected by the same disease were cured by a drug or nostrum, he immediately inferred that that drug or nostrum would cure all similar cases. The quack therefore proceeded by personal induction, and his methods gave rise to a system of therapeutic abstractions stemming from the purely visual facts of the case.

The scientific method, on the other hand, was just the opposite, procedure and performance being by deduction. The physician arrived at the facts through contemplation from the heights of his abstract knowledge. In treating disease, the cure was performed through a chain of abstractions. Concrete action in a particular case grew out of an abstruse concept of illness and some scattered ideas on therapy. Science was not individualized, and the fifteenth century physicians, hidebound by inflexible dogma, treated their patients by rule of thumb, forcing them to fit into the framework of their abstruse theories on medical practice. Today, the empirical methods, after careful examination by medical historians, appear to be much more

Calisto
Parmeno
Sempronio
Celestina
Aesto veo Melibea la gran
deza de dios. Me. en que cali
sto. La. en dar poder a natu-
ra que de tã perfeta hermosu
ra te dotasse: z fazer a mi ime-
rito tanta merced q̃ ver te al-
cãçasse: z en tan cõuenẽte lu-
gar q̃ mi secreto dolor mani-

Reproduction of part of a page from the second edition of *La Celestina* (1499). (Courtesy of the Library of the Hispanic Society of America, New York.)

practical and effective than the accepted "official" medical system of the fifteenth century. The former was an artless and rudimentary therapy based on a pseudo-scientific and popular medicine; the latter was a species of medical metaphysics in which the prevailing notions on body fluids and temperatures canceled the physician's intuition.

The basis of Celestina's character as a healer was a profound self-confidence and the trust she inspired in her patients. Sometimes she reached the heights of blatant showing off and theatrical braggartism, for this sort of byplay was an indispensable factor in the success of any self-respecting charlatan. The medieval physician considered himself completely trained once he had swallowed up the indigestible medical science of the Moslems. The quack, on the other hand, realized that he had to shape his personality to fit his clientele, and he therefore forged an inner core of flamboyance and tempered it in the light of his own immeasurable self-conceit.

As noted by Liek Danzing, that was the element lacking in many physicians, who, despite their learning, were unable to heal because an excess of criticism damped down their own personal initiative.

Celestina placed no reliance on science nor on drugs or incantations. She was as devoid of confidence in her own science as she was full of faith in her own power of suggestion and in the power of every living being to cure himself. Celestina was, in fact, as much a born psychologist as a quack.

Her poor opinion of surgeons, who were gaining importance in this period as anatomy gained scientific recognition, is evident in her words, "I rejoice at this news as much as a doctor does at scabs, and in the same way that he first makes the sores worse in order to increase his fees for the promise of recovery, so also do I reckon to work on Calixtus" ("*. . . me alegro de estas nuevas como los cirujanos de las descalabraduras, e como aquellos dañan en los principios las llagas e encarecen el prometimiento de la salud, asi pienso yo hacer a Calisto*"). Celestina is well aware of the tricks employed by any back-room physician of the time to exaggerate the gravity of a wound and thus increase his social renown and his financial rewards.

Deep in Celestina's medical conscience throbbed a complete lack of faith in the medicine of the time: "There is no greater clog on good health than abundance and variety in victuals . . . and a sore will never heal when so many remedies are there to be tried out" ("*No hay cosa que más la sanidad impida que la diversidad mundanza e variedad de los manjares . . . e nunca la llaga viene a cicatrizar, en la cual muchas melecinas se tientan*"). The following words summarize her complete disbelief in the effect of remedial cures: "as they say of the dipping-pool of Bethesda, where out of every hundred who go in, only one comes out properly cleansed" ("*. . . como se escriue de la probática piscina que de ciento que entrauan sanaba uno*"). At the bottom of this scepticism lies an unshakable belief in her own healing powers.

For the rest, Celestina possessed not only the empirical culture of the period but also a knowledge of sex determination in plants and of the habits of beasts: of the "unicorn who cringes when he spies a virtuous maiden" ("*unicornio que se humilla ante cualquier donzella*"), a fable already mentioned by Pliny and repeated in more modern times by Huerta and other writers; "of the dog that out of pity will not bite he who kneels in front of him, and the pelican that pierces her breast to feed her young" ("*del perro que por piedad no muerde a quien ante él se hecha al suelo, del pelícano que se rompe el pecho por mantener a sus hijos*"), which facts are confirmed by Valdecebro in his treatise titled "Birds."

CELESTINA'S ACHIEVEMENTS IN SURGERY

To her theoretical knowledge Celestina added the surgical activities already alluded to. All Toledo (Salamanca?) knew that she trafficked in maidens and then "restored their virginity in more than five thousand instances," as we are told in the play.

The whole practice of quacksalvers in the fifteenth century was built up on shady sexual intrigues, as was only to be expected in an era when aphrodisiacs and love philters were the mainstays of libidinous dealings. An age of prudery always produces

characters whose mission is to make a mockery of the harsh moral austerity surrounding them. Celestina or Don Juan could have never existed in ancient Greece or during the Renaissance, for they are the offspring of periods of intense sexual repression, such as existed in fifteenth century Spain.

Celestina herself on a certain occasion alludes to "the impotency she is able to bring about" by means of her charms and to the recoveries she can similarly effect. She is therefore past mistress in all the secrets of the complicated medieval control of sexual powers.

Her surgical stock in trade is limited but adequate for her requirements. A colored skillet, a few slender needles like those used by leatherworkers, and bits of waxed silk thread and catgut are all she needs for repairing the damages of illicit love affairs. She has to have roots of spikenard, bloodwort, red sumac, squills, and horsetail, styptic herbs and other astringents for stanching the flow of blood. This tackle is all she requires for getting away with the most audacious impositions on her clients, as, for instance, "on the occasion of the French Ambassador's visit" ("*cuando vino el embajador francés*") when, three times running, she sold as a "virgin" a lusty, buxom lass already well versed in the arts of harlotry.

THE PHARMACOLOGIC ARSENAL OF CELESTINA

It is, however, in the business of cosmetics and pharmacology that Celestina's greatest success lies. The entire medieval pharmacopoeia, as well as the purely empirical, was at her disposal. Celestina, however, suspicious of drugs, shared in the new tendency to resort to plants and more natural remedies.

Characteristic of this reaction was a book published sometime during the first three decades of the fifteenth century under the title *El menor daño de la Medicina* ("The Least Mischief in Medicine") by the learned physician Alphonso Chirino, "professor of medicine and physician extraordinary to His Highly Illustrious, Enlightened and Powerful Majesty King John II of Spain, mayor and supervisor of physicians and surgeons in His Majesty's Realms and Dominions" ("*profesor de medicina e físico del muy alto, esclarecido, muy poderoso Rey Don Juan el segundo, alcalde e examinador mayor de los físicos e cirujanos de sus Reigno e señorios*"). This work shows a naturalistic reaction against the writings of the Moslem colleges, the *praxis medicinalis*, and other medical works based on alchemy and chemistry popularized at the beginning of the fifteenth century by Arnold of Villanova. In this work, phrases such as the following occur: "Be assured that it is better to cure without medicines than with them. There is no shadow of doubt but that it is Nature herself and not the artificial remedies that effect the cure" ("*Sabe siertamente que es mejor sanar sin medicinas que con ellas . . . Tener sin duda que natura ha de sanar las enfermedades e no las melesinas*").

Celestina, the great disbeliever in drugs, neverthelesss kept handy the whole vast and varied battery of them, for she was well aware that common folk have a strong fancy for the mysterious concoctions in bottles and jars.

Like the soothsayers in their mansion mentioned in Apuleius, she kept in her shack a varied stock of perfume and cosmetic liquors, ointments, and creams such as those often mentioned by Pliny and Dioscorides. To all this she added herbs

for medicinal baths, so much in vogue among the Arabs. In another room she stored remnants of woodland creatures such as beaks, claws, skins, and hooves, as well as blood and fats from wild beasts, all brought to her by sundry peasants and others who, at her bidding, clambered up the thyme-scented mountains to hunt such birds and beasts.

Sometimes she resorted to black magic and stuck needles and pins into hearts made of wax. That such wonder-working practices coincide in various parts of the world and periods, as pointed out by Frazer in *The Golden Bough*, is confirmed by the practices of the witches in *Macbeth*, which corroborates Bastian's contention that there exists a common universal practice among peoples of different races but of a similar level of intelligence.

Skeptical though Celestina was about the power of her incantations, yet when her maid suffered from monthly pains, she advised her to first sniff some friendly odors and then, instead of the more usual course of devotions and prayers, to undergo a violent and erotic type of treatment. On the other hand, against toothache she prescribed a prayer to St. Apollonia, and here it is curious to note that the sufferer in question tells of trying to alleviate the pain by drumming out tunes with his fingers. Cure by music was already known to Hippocrates, who prescribed Corybantic songs as a remedy for melancholy. At a later date, Christopher Hufeland treated St. Vitus' dance by making his patients listen to Handel's oratorios, while Hunter in his turn treated cases of neuralgia with sonatas and fugues.

Celestina must be considered from all angles. Only then is it possible to understand her peculiar mental make-up and manifold activities so full of contradictions. She is no blind adherent to one particular dogma, nor is she tied down to some particular way of healing. She is aware of the effects obtainable with botanical medicines and cosmetics; she is completely amoral in her lecherous dealings; she practices witchcraft while keeping one foot within the Church—as a sop to the religious atmosphere of the times—among whose priests she has enough friends to assist her with prayers, and even she herself does not boggle on odd occasions to tell a rosary, though she does so rather as a matter of good business than from any true sense of devotion.

To appreciate Celestina's high repute, we must consider her environment and times, as well as her own particular personality. The fifteenth century in Spain represents a period of transition from the high-flown science of the Moslems to the more rationalized and scholastic learning of the sixteenth century, when people, hitherto accustomed to medicine padded out with the lyricism and fantasy of the Arab physicians, first came in contact with scientific anatomy.

The people's appetite, however, was not to be easily satisfied. They hankered after something else. They wanted their physicians (too busy in their thirst for scientific knowledge to do more than peer down at their patients from their ivory towers) to stretch out the hand of understanding and set working again those spiritual resources that might have been battered down during the course of their sickness. But the physicians of the period could not do this without endangering their professional prestige, and only practitioners of the falser arts, like Celestina, would undertake such a task.

The atmosphere of the times played a big part in Celestina's success. In the

lascivious underworld surrounding her, she had entry into all homes and all minds, enabling her to learn their secrets, which she could then use discreetly in her cures, applying herself more to the treatment of the ailing mind than of the body. Two further factors in her success were self-conceit and the knack of winning the patient's full confidence.

Nowadays, when biochemistry and microscopic research have somewhat mechanized the art of medicine, such an overrating of the personality of the healer may be incomprehensible. But, as Stefan Zweig said, "The desire for a guide and master lives and stirs inextinguishably in the human mind, eternally athirst for some miracle to happen."

Celestina, expert in lechery and artful in physics, appears on the transitional stage of the fifteenth century as a true sorceress who goes about rooting with bony fingers into the treasure house of popular tradition and comes out with a few of those nuggets of psychologic gold so vital to the art of healing. Celestina, in her complex character and multitudinous activities, crystallizes that empirical practice of medicine which was the historical subsoil underlying the hidden spring from which issued the first trickles that became, in time, the majestic river of Medicine in the Golden Age of Spain.

In the eyes of history, the greatest merit of Celestina—direct descendant of that Dame Trot who romps through the earthy pages of Juan Ruiz's *Libro del buen humor* ("Book of Good Humor")—is that she became a timeless model for all later witches, soothsayers, and quacks, for instance, those in Goya's *estampas* or in the pages of Theophile Gautier. And, above all, that she was the model for the famous witch queens of Andalusia, "La Cañizares" and Camacha de Montilla, immortalized in the *Coloquio de Cipión y Berganza*, a tale of two wise talkative dogs, by the masterly quill of Cervantes.

Note: All bibliographic references have been integrated in the text of this paper. The edition of "La Celestina" consulted by the author was published by "La Lectura," Madrid (Spain), in 1926.

GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports on papers delivered at current medical meetings in the United States and abroad.

Preliminary Observations on the Experimental Use of Elastic Synthetic Fabrics as Vascular Substitutes

Presented by ROBERT H. WHITTLESEY, M.D., J. WALLACE BLUNT, JR., M.D., AND STEPHEN S. HUDACK, M.D., (St. Luke's Hospital) before the Cleveland Academy of Medicine, Experimental Medicine Section and Society for Experimental Biology and Medicine, Cleveland Section, Cleveland, Ohio, November 21, 1955.

The search for synthetic fabrics to be used as vascular substitutes has been carried on because of the difficulty of obtaining and preserving homografts for these purposes and because of progressive degenerative changes occurring in aortic homografts. This work has been carried on by various groups. Synthetic fabrics employed included nylon, orlon, and dacron.

This report consists of general preliminary observations with no statistics available as yet regarding the various types of fabrics employed. The abdominal or thoracic aorta of a series of anesthetized dogs were replaced by anastomosing 14 different types of tubes from various materials. Most of the dogs survived the operative procedure if the time for anastomosis was limited to 20 to 25 minutes. Aortograms were subsequently taken; after a test period varying from 1 to 222 days, the dogs were reexplored, and the graft was excised and examined. The grafts were all graded for various properties, but no final report is available.

The seamless tubes were less likely to develop clots. If the tubes were pre-coated with a silicone product, there was diminished bleeding through the pores of the tubes. The ends of grafts made of nylon, dacron, orlon, or teflon could all be sealed with a hot wire to prevent them from fraying.

Seamless tubes braided of "elastic" nylon showed the best results in these early studies. Such tubes were elastic both lengthwise and circumferentially. The consistency of the material was such as to provide ease in suture, and no wrinkles developed.

After a period of time, endothelial growth over a layer of fibrous tissue has been observed both coming in from the ends of the tube, and through the mesh. In arterial homografts, the elastic is the only layer that persists, and, after a time, even this disappears.

Branched forms of tubes made of nylon and orlon are also available to be used at sites of bifurcation or branching of vessels. The various materials this group has employed include nylon, orlon, dacron, teflon, and vinyon N, treated by various processes. A future report should provide a better evaluation of these synthetic fabrics as vascular substitutes. (*The future report referred to was presented before the*

Central Surgical Association on Feb. 24, 1956, and will appear later this year in the AMA Archives of Surgery.)

Experimental Steroid Diabetes

Presented by DWIGHT J. INGLE, PH.D., (The Ben May Laboratory for Cancer Research) before the New York Diabetes Association, New York, N. Y., October 27, 1955.

Rats given a tube-fed diet twice daily and given subcutaneous injections of cortisone developed hyperglycemia and severe glycosuria. Partial control of the glycosuria was obtained with 100 units of protamine zinc insulin/rat/day, this representing insulin resistance. The controlling of steroid diabetes with insulin does not suppress nitrogen loss. Large doses of steroids or corticotropin are necessary for the induction of steroid diabetes: adrenocorticotropic hormone, 7 mg./day (injection of corticotropin every two hours during the day), given to animals on high carbohydrate fluid diet; or cortisone, 20 mg./day, given to animals on high fat, low carbohydrate diet. We do not know how long steroid diabetes can be maintained in the rat. On cortisone acetate, 5 to 10 mg./day, the diabetes has been found to last as long as six weeks. Rats so treated show considerable variation in metabolic behavior. Glycosuria may be severe in the beginning, then diminish and disappear, or it may be mild in the beginning, becoming severe later. Large doses of desoxycorticosterone acetate (1, 2, 5, and 10 mg.) in partially depancreatized animals produce an exacerbation of steroid diabetes with severe glycosuria. Progesterone in massive doses of 50 to 100 mg./day has the same effect.

In animals on a high carbohydrate diet, estrogens, 0.5 mg./day of stilbestrol given to partially depancreatized tube-fed rats, produce glycosuria. In normal animals the glycosuria is temporary. A combination of steroids, 1 mg. of stilbestrol and 1 mg. of cortisone, were found to induce a greater glycosuria than did cortisone alone. The liver glycogen level is increased as the dose of steroid is increased and at times parallels the amount of sugar lost by glycosuria.

Can stress cause an exacerbation of experimental diabetes? Many toxic agents were tested in mildly diabetic rats without the exacerbation of the diabetes, e.g., formalin injections of 0.25, 0.5, and 1.0 ml. doses, to cause adrenal hyperplasia. Exposure of partially depancreatized animals to cold, from 26 C. to 3 C., caused almost complete abolition of glycosuria. Aspirin decreases glycosuria in the depancreatized animal. Severe non-specific stress is not diabetogenic in the rat.

BOOK REVIEWS

Biological Effects of External Radiation. Edited by HENRY A. BLAIR. New York, McGraw-Hill Book Company, Inc., 1954, Pp. 508, illus, $7.00.

This is a summary of the studies made during World War II on the biologic effects of x-radiation and irradiation with neutrons. The first part of the book deals with the effects of single doses of whole-body x-radiation; the second part studies the effects of chronic x-radiation; and the last section is devoted to the effects of fractionated doses of fast neutrons.

Roentgen irradiation is reported with regard to its effects on the mortality of dogs, rats, and monkeys, pathologic changes, peripheral blood, and mutation rates of fruit flies. A section of particular interest to physicians is that dealing with the alterations of finger ridges among persons in frequent contact with roentgen apparatus.

Anatomy of the Human Body. HENRY GRAY. Twenty-sixth edition edited by CHARLES MAYO GOSS. Philadelphia, Lea & Febiger, 1954. Pp. 1480, illus. $16.00.

The twenty-sixth edition of this classic work has been considerably improved by altering the sequence of presentation to correspond more closely to the modern approach to the study of anatomy. The chapter on the peripheral nervous system has been rewritten, and all references to the autonomic nervous system have been considerably expanded.

Other notable changes are a practically new chapter on embryology, revised descriptions of microscopic anatomy of parts of the digestive system, and an expanded section on the heart. There are numerous new illustrations, and some of the older histologic sketches have been replaced with more modern drawings. The legends of all the 1202 illustrations have been reset in a larger and easier to read type. An interesting feature of this 1480 page volume is that the bookbinding was done in such a fashion that the book will remain open at almost any page.

Atlas der Haut- und Geschlechtskrankheiten (Atlas of Skin and Venereal Diseases). WALTER FRIEBOES AND WALTHER SCHÖNFELD. Stuttgart, Georg Thieme Verlag (Intercontinental Medical Book Corporation, New York 16, N. Y.), 1955. Ed. 2. Pp. 292, in color. $28.10.

The second edition of this remarkable atlas of skin and venereal diseases is even better than the first. It is probably the most complete and lavishly illustrated textbook of its kind, containing 469 illustrations, most of them in perfect color photography. The names of the various diseases are mostly in their Latin or Greek forms, thereby making it easy to recognize illustrations without knowing German. The text accompanying each picture is short but adequately descriptive. The venereal disease section includes syphilis and lymphogranuloma venereum, among other conditions. The book is clearly indexed for easy reference.

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